UNIVERSITÉ DU QUÉBEC À MONTRÉAL

SYNTHÈSE D'ORGANOBISMUTHANES HAUTEMENT FONCTIONNALISÉS ET LEURS APPLICATIONS DANS LA FORMATION DE LIENS C–C, C–N ET C–O

THÈSE

PRÉSENTÉE

COMME EXIGENCE PARTIELLE

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TABLE DES MATIÈRES

LISTE DES FIGURES

LISTE DES ABRÉVIATIONS, SIGLES ET ACRONYMES

Å	Angström
α	Alpha
AcOEt	Acétate d'éthyle
$AlCl_3$	Chlorure d'aluminium
aq.	Aqueux
Ar	Aryle
β	Bêta
Bi	Bismuth métallique
Bi(III)	Bismuth à l'état d'oxydation +3
Bi(V)	Bismuth à l'état d'oxydation +5
$BiBr_3$	Bromure de bismuth
$BiCl_3$	Chlorure de bismuth
$Bi(OTf)_3$	Triflate de bismuth
$Bi(NO_3)_3 \cdot 5H_2O$	Nitrate de bismuth pentahydraté
bipy	2,2'-Bipyridine
Boc	Di-carbonate de di-*tert*-butyle
*n*BuLi	*n*-Butyle lithium
Br	Brome
CH_2Cl_2	Dichlorométhane
CH_2I_2	Diiodométhane
CH_3CN	Acétonitrile
Cl	Chlore
CN	Nitrile

Cs_2CO_3	Carbonate de césium
Cu	Cuivre
CuBr	Bromure de cuivre
CuI	Iodure de cuivre
$Cu(OAc)_2$	Acétate de cuivre
$Cu(OPiv)_2$	Pivalate de cuivre
Cy_2NMe	*N*-diméthyldicyclohexylamine
DME	Diméthoxyéthane
DMF	Diméthylformamide
DMSO	Diméthylsulfoxyde
Et	Éthyle
Et_3N	Triéthylamine
Et_2Zn	Diéthylzinc
F	Fluor
FG	Functional group (groupement fonctionnel)
Fmoc	Chlorure de fluorénylméthoxycarbonyle
H	Hydrogène
HCHO	Formaldéhyde
HCl	Acide chlorhydrique
HetAr	Hétéroaryle
H_2O	Eau
H_2O_2	Peroxyde d'hydrogène
HRMS	Spectroscopie de Masse Haute Résolution (*High Resolution Mass Spectroscopy*)
I	Iode

IR	InfraRouge
K_2CO_3	Carbonate de potassium
KF	Fluorure de potassium
KOH	Hydroxyde de potassium
m	*Méta*
Me	Méthyle
MeMgBr	Bromure de méthyle magnésium
MeOH	Méthanol
Mg^0	Magnésium métallique
$MgSO_4$	Sulfate de magnésium
$NaBH_4$	Borohydrure de sodium
$NaHCO_3$	Hydrogénocarbonate de sodium
NaOH	Hydroxyde de sodium
Na_2SO_4	Sulfate de sodium
NMP	*N*-méthyl-2-pyrrolidone
NO_2	Groupement nitro
Nu	Nucléophile
o	*Ortho*
p	*Para*
Pd	Palladium
$Pd(PPh_3)_4$	Tetrakis(triphénylphosphine)palladium
$PhI(OAc)_2$	(Diacétoxy)iodobenzène
$PhNH_2$	Aniline
PPh_3	Triphénylphosphine
pK_a	Constante d'acidité

*i*Pr	*Iso*-propyle
*i*PrMgCl·LiCl	Complexe de chlorure d'isopropyle magnésium et de chlorure de lithium
RMN	Résonance Magnétique Nucléaire
sat.	Saturée
Sm	Samarium
S_N2	Substitution nucléophile d'ordre 2
SN_{Ar}	Substitution nucléophile aromatique
Tf	Triflate
THF	Tétrahydrofurane
TLC	"Thin Layer Chromatography" (Chromatographie sur couche mince
t.p.	Température de la pièce
X	Halogène

RÉSUMÉ

Le développement de nouvelles méthodologies de synthèse pour la formation de liens C–C, C–N et C–O est essentiel pour la préparation de molécules d'intérêt thérapeutique. Les organobismuthanes ont trouvé leur place dans le domaine de la chimie organique dû à leur réactivité unique, leur stabilité, leur faible coût ainsi qu'à leur tolérance aux groupements fonctionnels sensibles. Les organobismuthanes présentent une réactivité semblable à celle des organomercures, tout en étant non toxiques, permettant ainsi le développement de méthodologies plus respectueuses de l'environnement. La conception de complexes organométalliques de bismuth et leurs modifications ont été réalisées afin de les appliquer en réaction de couplage pour la formation de nouveaux liens. Premièrement, dans la formation de liens C–C, les complexes trialkylbismuthanes ont été couplés, par catalyse au palladium, à des 2-haloazines et diazines fonctionnalisées. À ce jour, cette méthode de couplage de trialkylbismuthanes sur des pyridines, pyrimidines, pyridazines et pyrazines est une des méthodes développées la plus complète. Par la suite, une méthode de couplage au palladium impliquant des triarylbismuthanes a été appliquée sur ce même type de substrats afin d'apporter une alternative aux méthodes déjà connues dans la littérature. Dans la formation de liens C–N, une amélioration de la réaction de *N*-arylation d'indoles, publiée par les professeurs Derek H.R. Barton et Jean-Pierre Finet en 1988, a été rapportée grâce au bismuth trivalent. A l'issu de cet article, une méthode de *O*-arylation de 1,2-aminoalcools *N*-protégés a été développée. Dans la continuité de la formation de liens C–O, de nombreuses solutions ont été rapportées dans la littérature pour la synthèse de diaryles éthers, notamment la réaction d'Ullmann, d'Evans, Chan et Lam ou encore de Buchwald. Cependant, ces méthodes comportent des limitations comme de hautes températures de chauffage, l'utilisation d'un excès de réactif organométallique/catalyseur ou encore l'utilisation de ligands complexes. De ce fait, une nouvelle méthode de synthèse de diaryles éthers a été développée avec l'utilisation de triarylbismuthanes fonctionnalisés. Finalement, la complexité des groupements fonctionnels sur l'organobismuthane a été poussée à son paroxysme et leurs réactivités ont été étudiées dans un dernier projet.

Mots-clés : Méthodologie, molécules d'intérêt, organobismuthanes, réactions de couplage, groupements fonctionnels

ABSTRACT

The development of new synthetic methodologies for C–C, C–N and C–O bond formation is essential for the preparation of therapeutic molecules. The organobismuthanes have found their place in the field of organic chemistry due to their unique reactivity, stability, low cost and their tolerance to sensitive functional groups. The organobismuthanes have a reactivity similar to organomercuric reagents while being non-toxic, allowing the development of environmentally friendly methodologies. The organometallic complexes of bismuth have been applied in cross-coupling reactions for the formation of new bonds. First, trialkylbismuthanes reagents were coupled under palladium catalysis, onto functionalized 2-haloazines and diazines, leading to C–C bond formation. For the moment, this cross-coupling reaction on pyridines, pyrimidines, pyrazines and pyridazines is one of the most comprehensive developed methods. Then, a palladium-catalyzed cross-coupling reaction involving triarylbismuthanes was applied on the same type of substrates in order to provide an alternative to existing methods found in literature. In the field of C–N bond formation, an improvement of the *N*-arylation reaction of indoles, published by Barton and Finet in 1988, was brought through the trivalent bismuth. Thanks to this article, a method of *O*-arylation of *N*-protected 1,2-aminoalcohols was discovered. Regarding C–O bond formation, many procedures have been reported in the literature for the synthesis of diaryl ethers, such as Ullman, Evans, Chan and Lam or Buchwald reactions. However, these methods have limitations such as the requirement of high temperatures, excess of organometallic reagent/catalyst or use of complex ligands. Therefore, a new method of synthesis of diaryl ethers has been developed with functionalized triarylbismuthanes. Finally, the complexity of the functional groups on the organobismuthane was pushed to its limit and complexes reactivities were studied in a last project.

INTRODUCTION

0. 1. Le bismuth

0. 1. 1. Généralités

Souvent confondu avec l'étain ou le plomb, le bismuth appartient à la famille des pnictogènes et constitue le 83ème élément du tableau périodique.1a En le séparant du plomb, c'est Claude Geffroy le Jeune qui découvrit le bismuth au 18ème siècle. Son utilisation est toutefois plus ancienne, puisque des études ont montré que les Incas s'en servaient déjà afin de fabriquer leurs couteaux.1a, 1b

De par son haut poids moléculaire, il est un des éléments chimiques les plus lourds du tableau périodique. De plus, il s'agit d'un métal très stable car à l'état métallique, il ne réagit ni avec l'air ni avec l'eau. La non-toxicité de certains réactifs de bismuth en fait un élément avec un statut que l'on considère comme "vert". En effet, il est employé dans de nombreux produits comme par exemple le Peptobismol, qui est un médicament contre les douleurs abdominales. Reconnus depuis de très nombreuses années pour leur non-toxicité, les composés de bismuth possèdent donc un avantage de taille pour leur usage en chimie médicinale ou encore en cosmétique.

La configuration électronique du bismuth correspond à [Xe] (4f)14(5d)10(6s)2(6p)3. Fait remarquable, les électrons célibataires sur sa couche de valence lui confèrent la propriété d'être le métal le plus diamagnétique de la classification périodique. D'après la théorie VSEPR, BiR3 contient un doublet non liant (AX3E1) justifiant la géométrie tétraédrique (m + n = 4) et l'angle inférieur à 109.5°. Un don ou un retrait d'électrons justifie les deux degrés d'oxydations possibles du bismuth : +III et +V. Le Bi(III) est connu pour être plus stable que son homologue Bi(V) dû à l'inertie du

doublet non liant et sa symétrie sphérique. Ces deux états d'oxydations confèrent au bismuth une réactivité toute particulière (Schéma 1).

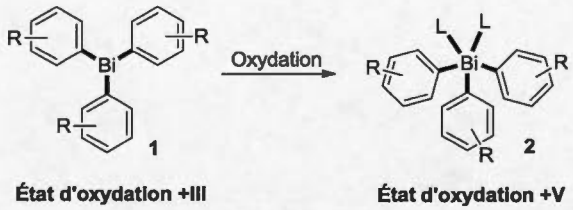

Schéma 1 : États d'oxydation du bismuth

Dans le cas de l'état d'oxydation +III, les groupements sur le bismuth possèdent un caractère nucléophile, donc les complexes trivalents réagiront avec des espèces de type électrophile. Par contre dans le cas de l'état d'oxydation +V, ils démontrent un caractère électrophile et réagiront plutôt avec des espèces de type nucléophile. Par conséquent, cet aspect unique du bismuth permet l'exploration d'un large éventail de réactions possibles avec les organobismuthanes.

0. 2. Applications du bismuth en chimie organique

Au cours du 20ème siècle, le bismuth connaît un intérêt croissant dû à une chimie riche.[2] Depuis une quinzaine d'années, le bismuth a été employé dans de nombreux types de réactions, que cela soit en tant que réactif organométallique ou en tant que catalyseur. Ces deux utilisations possibles du bismuth correspondent à des chimies complètement différentes, ce que nous allons démontrer par la suite. Premièrement, nous discuterons de son implication dans la chimie organique en tant que catalyseur et par la suite, de son rôle en tant que réactif possédant une liaison R–Bi.

0. 2. 1. Utilisation du bismuth en tant qu'agent activateur

Le bismuth a été grandement utilisé en tant que catalyseur dans de nombreuses et différentes méthodes durant ces dernières années. Nous citerons de manière non exhaustive l'étendue de son application dans ces réactions. La plupart des exemples cités ci-dessous sont issus d'une revue très complète écrite par Mohan dans *Chem. Soc. Rev.* en 2011.[1a]

0. 2. 1. 1. Utilisation du bismuth dans des réactions d'oxydation

Tout d'abord, le bismuth a été utilisé dans différents types d'oxydation. Nous allons en citer deux exemples.

Une méthode d'oxydation de thiol **3** en disulfide **4**, transformation importante du point de vue synthétique, avec du $Bi(NO_3)_3 \cdot 5H_2O$ a été proposée par Khodaei en 2003 (**Schéma 2**).[1a, 3]

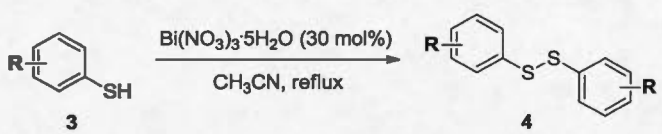

Schéma 2 : Oxydation de thiol **3** en disulfide **4** avec $Bi(NO_3)_3 \cdot 5H_2O$

Le faible coût du catalyseur permet de compenser la quantité importante de celui-ci utilisée dans cette transformation. Également, que les thiols soient de type aromatiques ou aliphatiques, l'oxydation en disulfides se fait toujours avec d'excellents rendements. De plus, les auteurs ont démontré que des alcools primaires étaient tolérés dans ces conditions d'oxydation, ce qui est un réel avantage dans la synthèse de molécules fonctionnalisées.

Le nitrate de bismuth pentahydrate a été également utilisé en tant qu'oxydant dans une méthode d'oxydation d'aldéhyde en acide carboxylique au micro-ondes, développée par Mukhopadhyay et Datta (**Schéma 3**).[1a, 4]

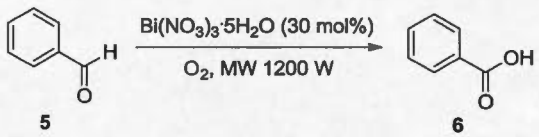

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Schéma 3 : Oxydation d'aldéhyde aromatiques **5** en acide carboxylique **6** impliquant $Bi(NO_3)_3 \cdot 5H_2O$

L'oxydation de cet aldéhyde aromatique en acide carboxylique correspondant nécessite que la réaction opère au micro-ondes et en présence d'oxygène. Ces conditions particulières permettent d'obtenir de très bons rendements ainsi que des temps de réactions plus courts comparativement à la méthode d'oxydation des aldéhydes en acides carboxyliques utilisant 30% H_2O_2 catalysé par l'anion Preyssler,[5] $[NaP_5W_{30}O_{110}]^{14-}$.

0. 2. 1. 2. Utilisation du bismuth dans des réactions de réduction

Le bismuth a également été utilisé dans de nombreuses réactions de réduction. En effet, en 2003, une méthode de réduction d'azoture en amines dans l'eau en utilisant du zinc métallique et $AlCl_3$ ou $BiCl_3$ comme acide de Lewis suivant les composés à réduire a été développée par Li. Les conditions proposées dans cet article permettent d'effectuer cette transformation avec des temps de réaction très courts et des rendements optimaux.[1a, 6] Une année plus tard, une déshalogénation, plus respectueuse de l'environnement comparativement à d'autres réactions de ce type, de composés α-halocarbonyles **7**, avec chlore et brome comme halogène, en milieu aqueux et en présence de bismuth a été rapportée par Lee et Chan (**Schéma 4**).[1a, 7]

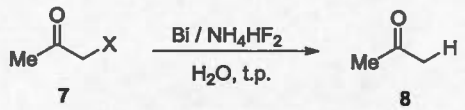

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Schéma 4 : Déshalogénation de composés α-halocarbonylés **7**

Dans cette réaction, le bismuth métallique est activé par le bifluorure d'ammonium, NH_4HF_2. Les auteurs ont remarqué que de nombreux métaux, mis en présence de ce réactif en milieu aqueux, pouvaient devenir très réactifs et c'est pour cette raison qu'ils se sont intéressés au bismuth, qui lui est parfaitement stable dans ces conditions de réaction. Le mécanisme d'action du bifluorure d'ammonium n'est pas connu dans le cas de l'utilisation avec le bismuth mais avec d'autres types de métaux, des transferts d'électrons libres ont été observés à la surface du métal afin de générer un radical anion en tant qu'intermédiaire de réaction. Un des avantages de cette réaction est qu'elle est chimiosélective. En effet, la présence d'un groupement NO_2 ou encore d'un carbonyle est tolérée.

0. 2. 1. 3. Utilisation du bismuth dans des réactions de protection/déprotection de groupements fonctionnels

De nombreuses méthodes ont été rapportées concernant la protection et la déprotection de groupements fonctionnels impliquant le bismuth et il serait difficile de toutes les citer. Par exemple, il est possible de protéger une amine, un alcool ou un phénol avec un Boc en présence de bismuth.[8] Également, la déprotection d'un Boc sur un aminoacide ou un peptide peut se faire de manière sélective en utilisant du $BiCl_3$.[9] Le triflate de bismuth $Bi(OTf)_3$ a aussi été utilisé en tant que catalyseur dans une réaction d'estérification d'acide carboxylique **9**, dans un solvant de type polaire protique (**Schéma 5**).[1a, 10]

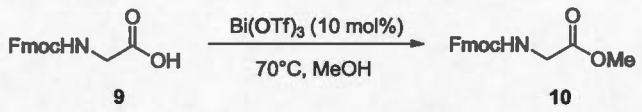

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Schéma 5 : Estérification d'acide carboxylique **9** impliquant $Bi(OTf)_3$

L'utilisation ingénieuse du $Bi(OTf)_3$ en tant que précurseur sécuritaire du réactif CF_3SO_3H, qui est corrosif et difficile à manipuler, a permis de développer une méthode simple d'application pour la synthèse d'esters. Dans ces conditions de réaction, le groupement protecteur Fmoc sera toléré, contrairement au groupement Boc qui lui sera clivé.

0. 2. 1. 4. Utilisation du bismuth dans la chimie des sucres

L'utilisation du bismuth est également observée en chimie des sucres, et notamment lors de la fonctionnalisation de monosaccharides permettant ainsi la construction de centres stéréogéniques très utiles dans ce type de chimie et en synthèse totale.

La glycosylation d'un glycoside diméthylphosphite **11** grâce au $BiCl_3$ en tant qu'agent activateur, a permis d'obtenir une mélange d'anomères du cyclohexylglucoside **12** (**Schéma 6**).[1a, 11]

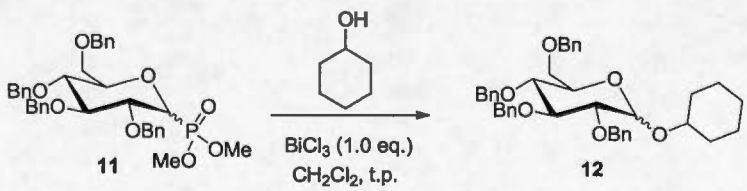

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Schéma 6 : Synthèse de cyclohexylglucoside **12**

0. 2. 1. 5. Utilisation du bismuth dans des réarrangements

Le bismuth a été appliqué dans de nombreux réarrangements de type Ferrier,[12] Fries,[13] Wagner-Meerwein,[14] Baylis-Hillman[15] ou encore dans l'aromatisation de

Hantzsch.[16] Le triflate de bismuth a été appliqué de manière efficace à l'oxydation de Baeyer-Villiger par Adapa en 2003 (**Schéma 7**).[1a, 17]

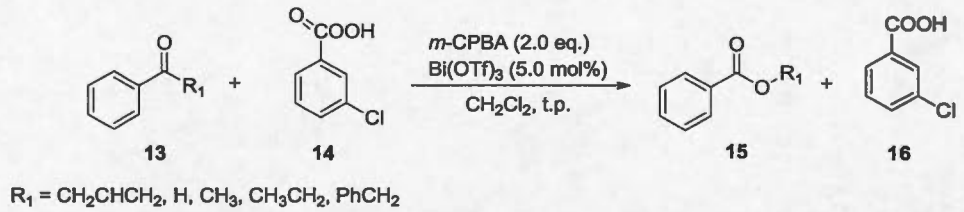


Schéma 7 : Oxydation de Baeyer-Villiger impliquant $Bi(OTf)_3$

L'utilisation du triflate de bismuth en tant que catalyseur comprend plusieurs intérêts majeurs, comme une récupération et une réutilisation du catalyseur sans altération de son efficacité ainsi que l'augmentation significative du temps de la réaction par rapport à la réaction de Baeyer-Villiger réalisée sans catalyseur.

Également, avec ce même catalyseur de bismuth, une réaction inattendue a été mise à jour lors de la tentative de réarrangement de Beckmann avec l'oxime de la 6-méthoxyindanone **17** (**Schéma 8**).[1a, 18] Au lieu d'obtenir l'amide cyclique attendu, une cyclopentanone **18** ainsi que son homologue α-tosylé **19** sont les produits majoritaires de cette transformation.

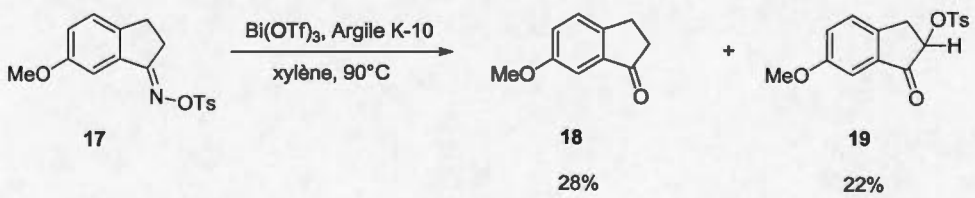


Schéma 8 : Réarrangement inattendu avec la 6-méthoxyindanone oxime **17**

De plus, le bismuth a été engagé, pour la formation de liens C–C, dans des réactions de Mannich,[19] des condensations d'aldols,[20] des acylations de Friedel-Craft[21] ou encore dans des réactions de Diels-Alder.[22]

0. 2. 1. 6. Utilisation du bismuth dans des réactions de formation de liens C–C

La création de liens C–C impliquant le bismuth a été une des voies les plus développées avec ce métal. Par exemple, une méthode d'éthérification intramoléculaire et sélective d'aldéhydes et cétones de dérivés d'éthers silylés **20**, impliquant une quantité catalytique de $BiBr_3$, pour la synthèse de tétrahydropyranes *cis*- et *trans*-2,6-di et tri-substitués a été rapportée par Evans (**Schéma 9**).[1a, 23]

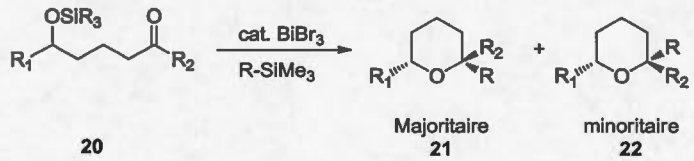


Schéma 9 : Synthèse de tétrahydropyranes *cis*- et *trans*-2,6-di et tri-substitués **21** et **22** impliquant $BiBr_3$

Un des plus grands avantages de cette méthode est sa sélectivité. En effet, le composé tétrahydropyrane **21** formé à l'issu de la cyclisation est largement majoritaire, dû à la faible réactivité du carbonyle protoné qui, lors de l'addition du réactif triorganosiloxy, permet de former l'ion oxocarbénium le plus réactif.

Le bismuth a aussi été appliqué à la réaction de Reformatsky, permettant l'obtention de composés β-hydroxycarbonyles de manière efficace. En effet, une réaction de Reformatsky, à partir de α-bromoacétophénone **23** et d'aldéhydes **24** en présence de $Sm/BiCl_3$, a été rapportée par Zhang et Zhang (**Schéma 10**).[1a, 24]

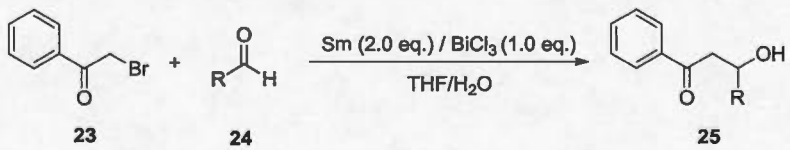


Schéma 10 : Réaction de Reformatsky de α-bromoacétophénone **23** impliquant $Sm/BiCl_3$

Le mécanisme de cette réaction n'a pu être élucidé de manière irréfutable. Cependant les auteurs supposent qu'une espèce acyle bismuth, générée par réaction entre α-bromoacétophénone **23** et le Bi(0), serait le réactif clé de cette transformation.

0. 2. 1. 7. Utilisation du bismuth dans des réactions de formation de liens C–O

De par son rôle d'acide de Lewis, $BiCl_3$ permet entre autre la création de liaisons C–O. Supporté sur silice, il a notamment été utilisé par Ahmed et Ansari pour l'isomérisation de la chalcone 2'-hydroxy substituée **26** en flavanone correspondante **27 (Schéma 11)**.[1a, 25]

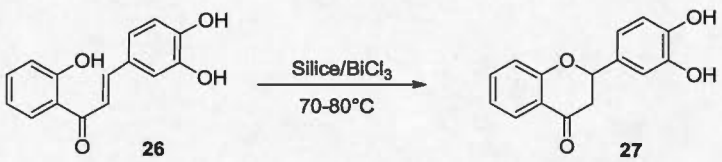


Schéma 11 : Cyclisation de la chalcone **26** en falvanone **27** impliquant $BiCl_3$ supporté sur silice

Les flavanones sont généralement obtenues par isomérisation de l'hydroxy chalcone correspondante en conditions acides ou basiques. Cependant, la plupart de ces méthodes procèdent avec de faibles rendements dû à l'équilibre entre ces deux espèces. Or les auteurs de cet article ont réussi à trouver des conditions suffisamment efficaces pour déplacer cet équilibre fragile vers la formation de la flavanone.

0. 2. 1. 8. Utilisation du bismuth en synthèse asymétrique

Les exemples utilisant le bismuth en synthèse asymétrique sont limités. En effet, nous n'avons pu trouver que quelques exemples de ce type dans la littérature. Une hydroxyméthylation asymétrique d'énolates de silicium **28** catalysée par $Bi(OTf)_3$ et une bipyridine chirale en solution aqueuse a été développée par Kobayashi en 2005 **(Schéma 12)**.[1a, 26]

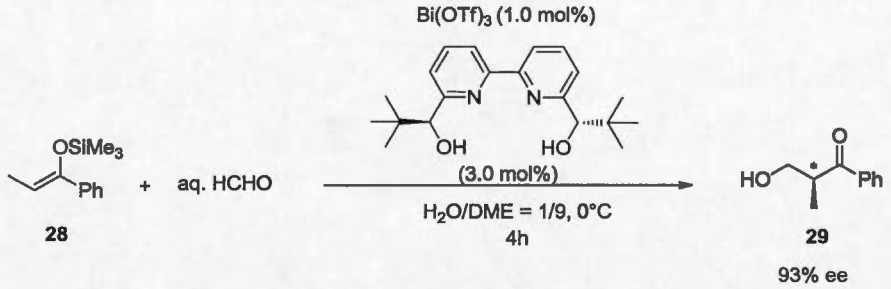


Schéma 12 : Hydroxyméthylation asymétrique d'un énolate de silicium **28** catalysée par $Bi(OTf)_3$ et d'un ligand bipyridine chiral

En général, les réactions avec des acides de Lewis chiraux en milieu aqueux sont extrêmement rares car ceux-ci se décomposent très rapidement en présence d'eau. Or, bien qu'il soit connu que $Bi(OTf)_3$ s'hydrolyse dans l'eau, dans ce cas-ci, il est stabilisé par le ligand chiral bipyridine basique. Dans ces conditions opératoires, la transformation s'opère avec d'excellents rendements, une très bonne sélectivité et il s'agit de l'une des premières réactions énantiomériquement contrôlées par un catalyseur chiral de bismuth en milieu aqueux.[1a, 27]

Comme nous l'avons démontré, le bismuth a été grandement utilisé ces quinze dernières années dans de très nombreux domaines de la chimie, notamment dans un rôle de catalyseur de réaction. À présent, nous allons discuter de sa place en tant que composé organométallique dans la chimie organique. Plusieurs exemples cités ci-dessous sont issus d'une revue très complète écrite par Condon dans *Organic Preparations and Procedures International* en 2014.[28a]

0. 2. 2. Utilisation du bismuth en tant que réactif organométallique

0. 2. 2. 1. Formation de liens C–C catalysée au palladium avec Ar_3Bi

La formation de liaisons C–C par couplage croisé catalysé au palladium est l'une des transformations chimiques les plus importantes en chimie organique pour la

formation de molécules cibles. En effet, son étendue a été démontrée en 2010, lors de la remise du prix Nobel de chimie aux professeurs Ei-ichi Negishi, Richard Heck et Akira Suzuki, pour leur contribution exceptionnelle à la découverte des réactions du même nom. Ces méthodes sont parmi les réactions les plus répandues et les plus efficaces pour la création de nouveaux liens C–C. Les réactions de type Heck, qui permettent la fonctionnalisation de doubles liaisons terminales, ont été décrites pour la première fois en 1973.[28a, 29] Une réaction semblable à la réaction de Heck a été appliqué aux organobismuthanes quelques années plus tard par Kawamura, qui a découvert la fonctionnalisation du oct-1-ène avec l'acrylate d'éthyle et le triphénylbismuth.[28a, 30] Dans le domaine de la chimie du bismuth catalysée au palladium, la formation de molécules symétriques de type biaryles, grâce aux triarylbismuthanes, a été rapportée pour la première fois en 1988 par Barton.[28a, 31] Ce type de réaction s'effectue en présence d'un catalyseur au palladium ce qui permet, contrairement à la catalyse au cuivre, le transfert des trois groupements aryles portés par le bismuth ainsi qu'une économie d'atomes. Un exemple de ce type de méthode de couplage biarylique a été proposé par Uemura (**Schéma 13**).[28a, 32]

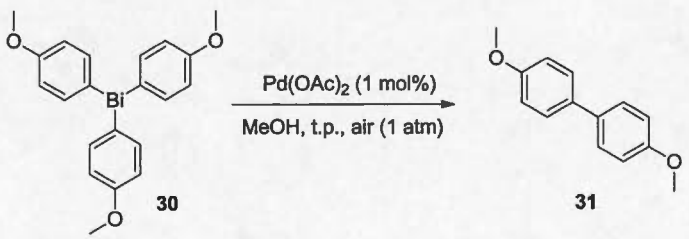


Schéma 13 : Synthèse du biaryle **31** à partir de *p*-méthoxybismuthane **30** et de $Pd(OAc)_2$

Les réactions de couplage de réactifs de bismuth trivalents peuvent également se faire avec des halogénures (X = Br ou I) ou des triflates d'aryles. En 2001, Rao et Shimada en ont d'ailleurs démontré l'étendue ainsi que les limitations.[28a, 33] Leurs conditions de réaction nécessitent l'utilisation catalytique du $Pd(PPh_3)_4$ et d'un léger excès de

ArX (3.25 eq.) par rapport au Ar_3Bi étant donné que les trois groupements aryles sur le bismuth transfèrent. Le couplage sur des hétéroaryles de type pyridine a également été rapporté **(Schéma 14)**.

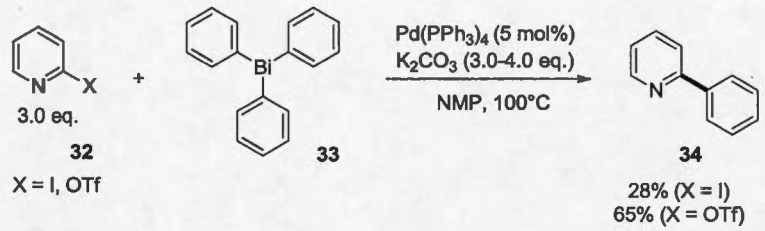


Schéma 14 : Arylation d'une 2-halogénopyridine **32** catalysée au palladium impliquant Ph_3Bi **33**

La tolérance de cette réaction aux groupements fonctionnels sensibles de type cétone ou aldéhyde a été démontrée par Wang. La spécificité de cette réaction est que le catalyseur de palladium est supporté sur du polystyrène, avantage non négligeable dans un contexte de chimie verte où le recyclage du catalyseur est un point essentiel **(Schéma 15)**. [28a, 34]

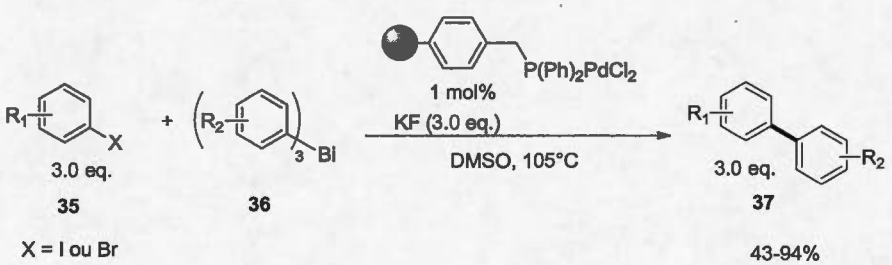


Schéma 15 : Arylation d'halogénures d'aryles **35** avec des organobismuthanes substitués **36** catalysée par du palladium supporté sur du styrène

0. 2. 2. 2. Formation de liens C–N catalysée au cuivre avec Ar_3Bi

L'utilisation des Ar_3Bi, en tant qu'agents d'arylation dans la formation de liaisons C–N et C–O est connu depuis de nombreuses années, notamment avec les méthodes

de Barton[28b] et Chan[35] que nous aborderons pour situer le contexte. Par la suite, nous passerons en revue les nouveaux développements, apportés à cette chimie depuis 2001.[28a]

Dès 1986, Barton a développé des réactions de *N*-arylation d'amines aliphatiques et aromatiques mettant en jeu un triarylbismuth diacétate, $Ar_3Bi(OAc)_2$, un réactif de bismuth pentavalent, en présence de cuivre métallique. Il a ensuite étendu cette méthode à l'utilisation de bismuth trivalent avec l'acétate de cuivre, permettant la formation du complexe pentavalent in-situ (**Schéma 16**).[28a, 28b] Bien que dépendante de l'encombrement stérique et de la basicité de l'amine, cette réaction reste une méthode efficace pour la synthèse d'amines secondaires.

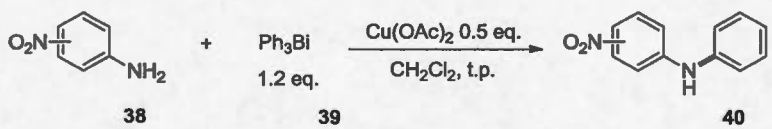


Schéma 16 : *N*-Arylation d'amines aromatiques **38** catalysée par $Cu(OAc)_2$ impliquant Ph_3Bi **39**

Près de dix années plus tard, Chan a amélioré cette méthode par l'introduction d'une amine tertiaire comme la pyridine ou la triéthylamine en tant que catalyseur de réaction, permettant la *N*-alkylation d'une plus large gamme de composés, tels que des amides, imides, urées, carbamates et sulfonamides avec de très bons rendements.[28a, 35]

Ce type de réaction a notamment été appliqué à la synthèse d'une molécule naturelle, un inhibiteur du cholestérol **42**. Cette molécule a pu être préparée par *N*-arylation d'une 2-pyrazoline **41** (**Schéma 17**) catalysée par du $Cu(OAc)_2$ avec un triarylbismuthane en tant qu'agent alkylant.[28a, 36]

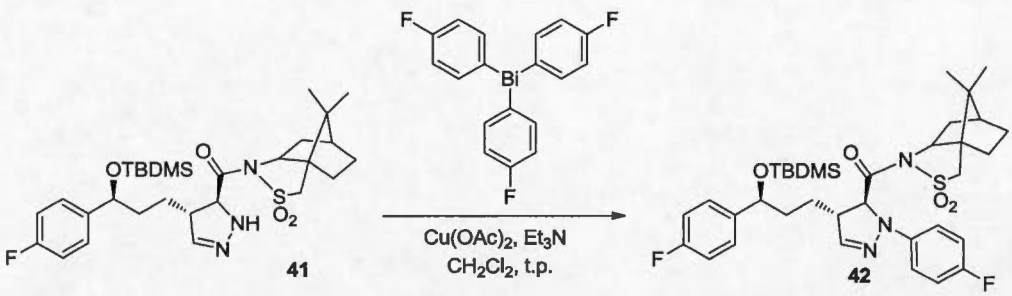


Schéma 17 : Synthèse d'un inhibiteur du cholestérol **42** par *N*-arylation d'une pyrazoline **41** impliquant un organobismuthane

Comparativement aux *N*-arylations catalysées au palladium, celles impliquant du cuivre possèdent l'avantage de tolérer des groupements complexes tels que l'imide ci-dessus.

Dans des conditions de réactions très semblables, l'arylation d'hydrazines tri-protégées a été rapportée par Mäeorg et Ragnarsson (**Schéma 18**).[28a, 37-39]

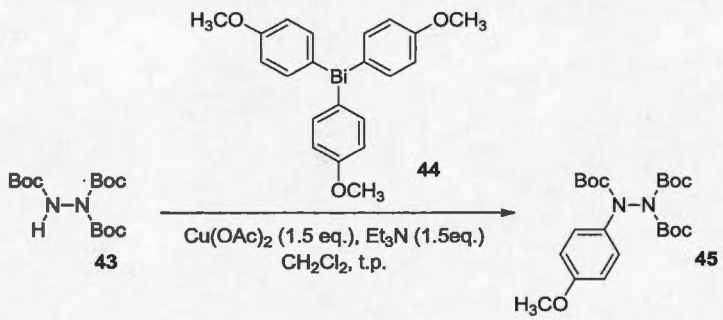


Schéma 18 : *N*-Arylation de l'hydrazine **43** catalysée au cuivre impliquant le *p*-méthoxybismuthane **44**

Comme dans le cas de la réaction de Barton, cette transformation est très sensible à l'encombrement stérique, ici notamment du réactif organobismuthane. En effet, la réactivité de quelques *ortho* triarylbismuthanes a été testée avec ces hydrazines et il a

été observé que des conditions opératoires plus poussées sont nécessaires pour obtenir des résultats satisfaisants.

0. 2. 2. 3. Formation de liens C–O catalysée au cuivre avec Ar_3Bi

Les organobismuthanes trivalents ont été utilisés à quelques reprises dans des réactions de *O*-arylation d'alcools et de phénols. Cependant, les réactions de *O*-arylation utilisant des organobismuthanes sont moins nombreuses dans la littérature que les réactions de *N*-arylation. À titre d'exemple, l'arylation d'alcools aliphatiques **38** en présence d'acétate de cuivre a notamment été rapportée par Dononov en 1995 (**Schéma 19**).[28a, 40]

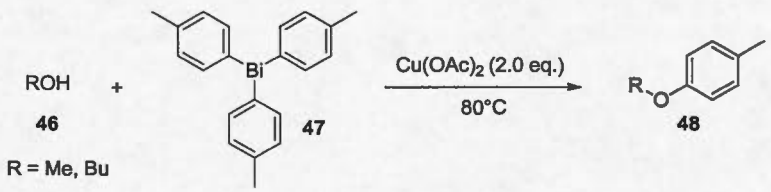


Schéma 19 : *O*-Arylation d'alcools aliphatiques **46** catalysée au cuivre impliquant le *p*-méthylbismuthane **47**

Dans cette transformation, le triarylbismuthane passe de l'état d'oxydation +3 à l'état d'oxydation +5 grâce à l'acétate de cuivre. D'autres agents d'oxydation tels que diacétate d'iodobenzène,[41] le peroxyde de benzoyle[42] et l'OXONE®[43] sont également connus pour oxyder les réactifs de bismuth trivalents en réactifs pentavalents. De plus, une réaction de transfert d'aryles sur des alcools de type secondaire impliquant des triarylbismuthanes et de l'OXONE® a été rapporté par Sheppard (**Schéma 20**).[28a, 43]

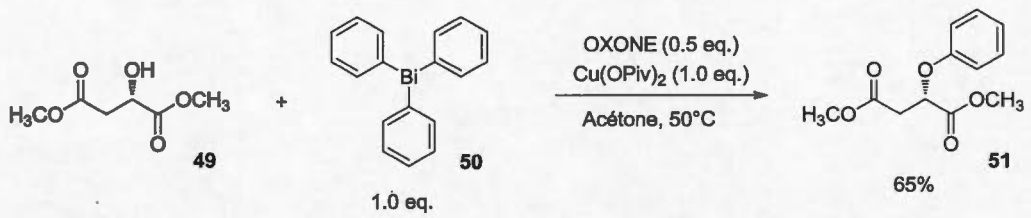


Schéma 20 : Réaction de transfert d'aryle sur l'alcool **49** à partir d'organobismuthane en présence d'OXONE® et de pivalate de cuivre

Concernant l'arylation d'alcools tertiaires, une méthode impliquant l'utilisation d'iodobenzène diacétate en tant qu'agent oxydant du réactif de bismuth a été découverte par Sato (**Schéma 21**).[28a, 44] Dans cette réaction, une quantité catalytique de cuivre est nécessaire, tout comme la présence d'oxygène afin de ré-oxyder le catalyseur. Un milieu anhydre permet aussi d'obtenir des rendements optimaux. Dans le cas de ces alcools tertiaires aliphatiques et dans de nombreux exemples dans la formation de liens C–O catalysée au cuivre, l'encombrement stérique en position *ortho* sur l'aryle à transférer est le point faible de cette transformation.

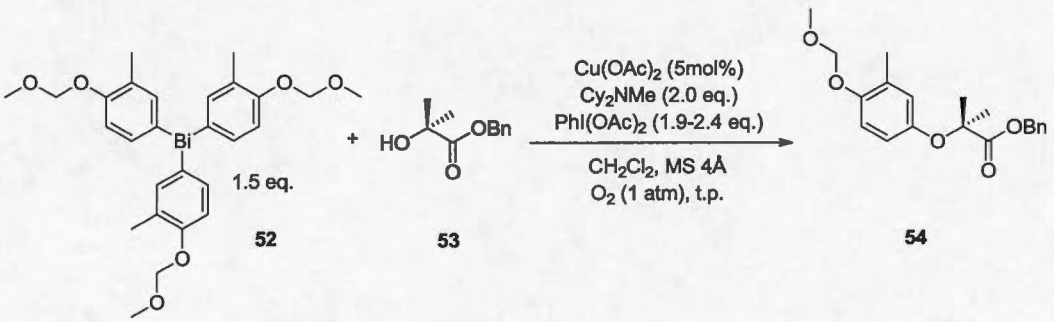


Schéma 21 : Arylation de l'alcool tertiaire **53** catalysée au cuivre impliquant un réactif de bismuth **52**

Le développement de nouvelles réactions chimiques avec de nouveaux métaux moins toxiques tels que le bismuth est un défi innovant à relever à l'ère du respect envers l'environnement. Les organobismuthanes présentent de nombreux avantages en plus

de leur non-toxicité. En effet, leur faible coût ainsi que leur grande tolérance à la plupart des groupements fonctionnels sensibles en font des réactifs de choix.

0. 2. 3. Le bismuth et les autres métaux

Tout comme les autres métaux, le bismuth est un élément important dans les couplages organométalliques. En effet, les organomagnésiens et les organozincs sont des espèces très sensibles à l'air et à l'eau, ce qui nécessite de nombreuses précautions pour leurs utilisations. En ce qui concerne les organomercuriques et les organoétains, ils sont de moins en moins utilisés en raison de leur grande toxicité. De nos jours, les couplages organométalliques impliquant les acides boroniques représentent la part la plus importante des réactions de couplage au palladium. Effectivement, leur tolérance aux groupements fonctionnels, leur stabilité ainsi que leur coût modéré en font des réactifs de choix. Cependant, la nécessité d'optimisation des conditions de réaction peut être incommodante. Une alternative relativement récente aux acides boroniques sont les organoindiums. Ces composés possèdent de nombreux atouts comme une très bonne stabilité, une facilité de mise en œuvre des réactions et une bonne tolérance aux groupements fonctionnels. Toutefois, leur coût relativement élevé restreint leur utilisation. Finalement, les organobismuthanes se placent en tant qu'organométalliques de prédilection au vu de leur très grande stabilité à l'air et à l'eau, leur faible coût, leur bonne tolérance aux groupements fonctionnels et leur facilité d'utilisation.[45]

0. 3. Synthèse et modification des organobismuthanes

La synthèse et la modification de réactifs organobismuthanes est l'une des majeures parties de cette thèse. En effet, contrairement à d'autres métaux comme le magnésium, il est possible de fonctionnaliser ces composés avec des groupements réactifs tels que des aldéhydes, des alcools, des esters, etc. Cette famille de composés organométalliques peut par la suite être utilisée dans différentes réactions de couplage

au palladium ou au cuivre pour permettre la création de liens C–C, C–N et C–O (**Schéma 22**).

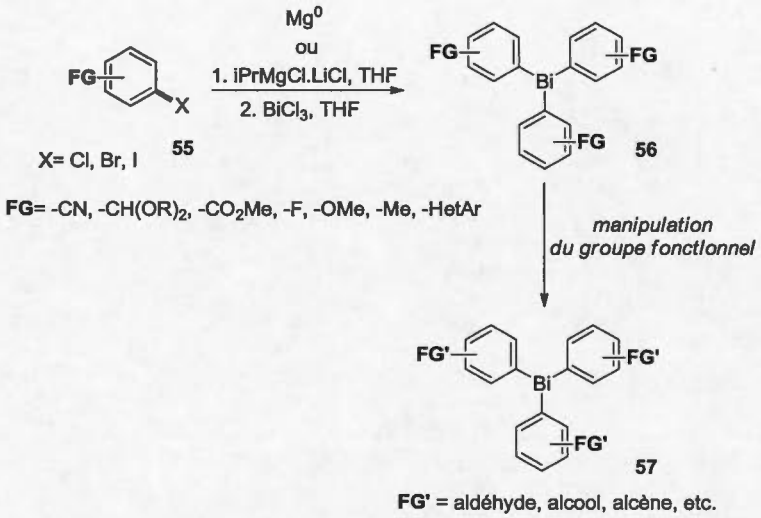


Schéma 22 : Synthèse et modification de réactifs organobismuthanes

Les réactifs de bismuth sont facilement synthétisés à partir des organomagnésiens correspondants par addition sur le chlorure de bismuth. Selon la nature du groupement fonctionnel porté par l'halogénure d'aryle de départ, il n'est pas toujours possible de préparer le magnésien par la méthode classique, c'est-à-dire avec le magnésium métallique chauffé au reflux du THF. Lorsqu'un groupement fonctionnel sensible est présent tel qu'un groupement nitrile ou ester, on utilise alors la méthode de Knochel[46] basée sur le complexe de chlorure d'isopropyle magnésium et chlorure de lithium qui permet un échange métal-halogène entre l'alkyle magnésium et l'halogénure d'aryle. Une fois le magnésien préparé, celui-ci effectue une réaction de transmétallation sur le chlorure de bismuth pour fournir le réactif de bismuth correspondant qui peut alors être utilisé directement dans des réactions de couplage subséquentes. Alternativement, ce composé peut être modifié afin d'obtenir d'autres types de réactifs organométalliques élaborés comportant des groupements fonctionnels difficilement accessibles par des méthodes classiques. Pour explorer le

potentiel des organobismuthanes dans le transfert de groupements fonctionnels hautement fonctionnalisés, nous avons préparé des réactifs "classiques" soit par la méthode de Grignard soit par celle de Knochel (**Schéma 23**).

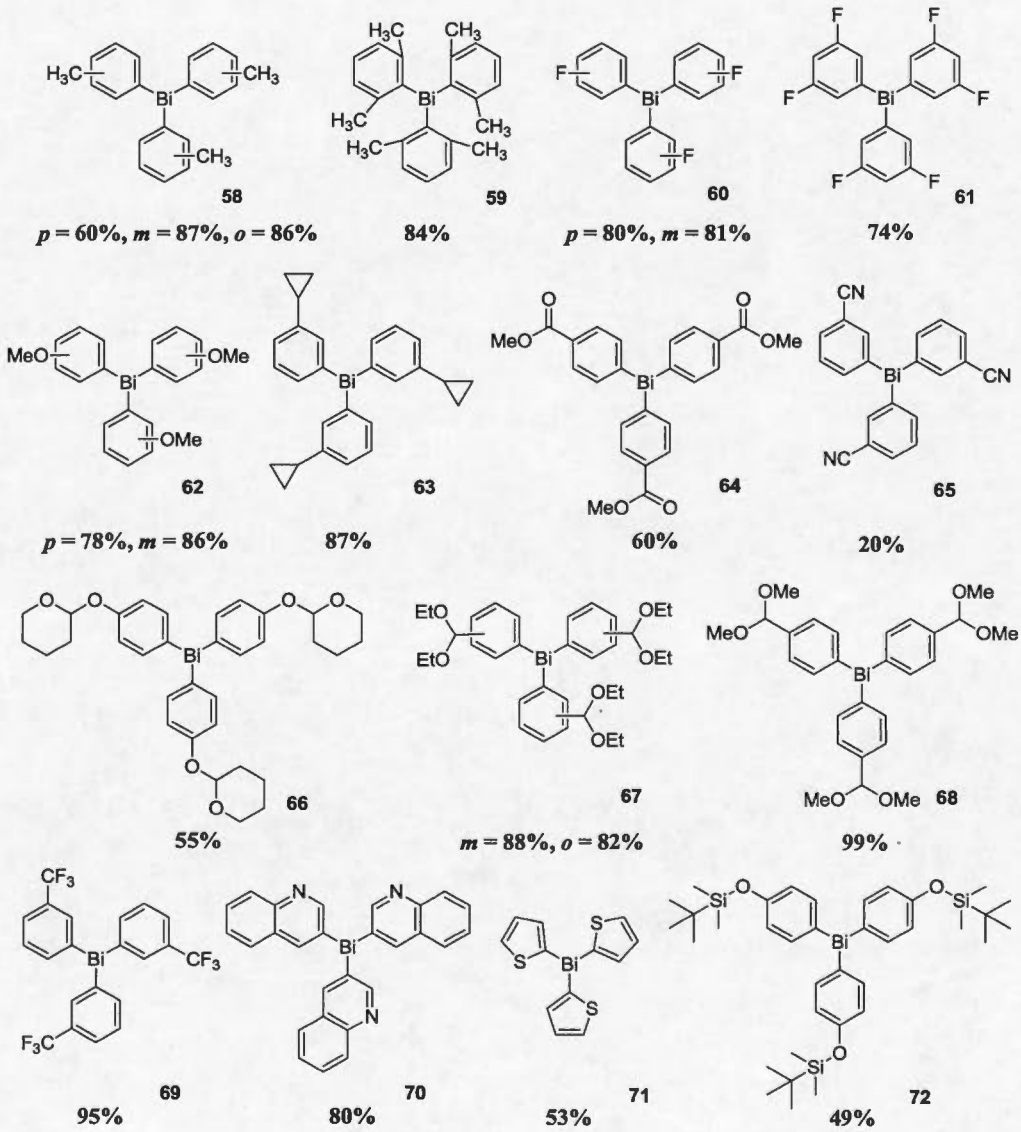


Schéma 23 : Synthèse des triarylbismuthanes "classiques"

De nombreux composés portant des groupements neutres, attracteurs et donneurs d'électrons, des groupements plus sensibles comme un ester et un nitrile, deux types d'acétals, des hétérocycles, un éther de silyle, etc., ont pu être synthétisés. Après la synthèse des organobismuthanes par voie classique, nous avons pu réaliser la préparation de réactifs hautement fonctionnalisées. Étant donné l'impossibilité de synthétiser ces composés par la méthode de Grignard, nous avons envisagé la manipulation de groupements fonctionnels directement sur le métal (**Schéma 24**).

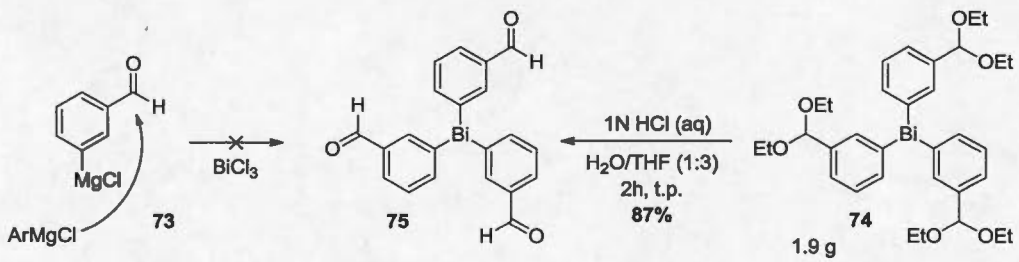


Schéma 24 : Préparation du *tris*-formylphénylbismuth **75** par manipulation du groupement fonctionnel acétal

L'acétal **74** a été placé en solution aqueuse et acide, et le composé **75** portant un aldéhyde a été obtenu dans un rendement de 87% à l'échelle du gramme. Il est important de rappeler que puisque le bismuth est un métal, les organobismuthanes font donc partie de la classe des composés organométalliques, c'est-à-dire des composés comportant une liaison carbone–métal. Il est assez rare qu'un composé organométallique supporte de telles conditions de réaction car en général, l'hydrolyse du lien carbone-métal est observée.[47] L'obtention du *tris*-formylphénylbismuth **75** a été confirmée par RMN, HRMS, IR mais également par diffraction des rayons X (**Schéma 25**) afin de démontrer la présence des trois groupements aromatiques sur le bismuth ainsi que l'arrangement dans l'espace de ces derniers.

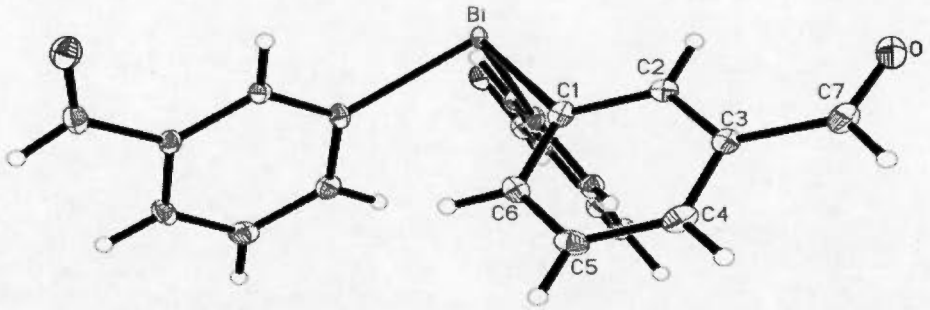


Schéma 25 : Structure ORTEP du *tris*-formylphénylbismuth **75**

La recristallisation de **75** et la diffraction des rayons X ont révélé que le composé est de structure pyramidale, que l'angle C–Bi–C est de 92.02° et que les longueurs de liaison C–Bi sont de 2.266 Å. La structure montre clairement la présence des trois groupes aryles portant chacun un groupement formyle. Cette conformation particulière des trois aromatiques est possiblement dû à la présence du doublet libre du bismuth qui, par répulsion électronique, contraint les cycles à ce positionnement particulier. Toutefois, des études computationnelles sont requises afin de comprendre l'origine de cette géométrie particulière.

Par la suite, d'autres modifications de groupements fonctionnels ont été effectuées. Premièrement à partir du *tris*-formylphénylbismuth **75**, une réaction d'addition de Grignard, de réduction au $NaBH_4$ et des réactions de type Wittig et Horner-Emmons-Wadsworth ont été réalisées (**Schéma 26**).

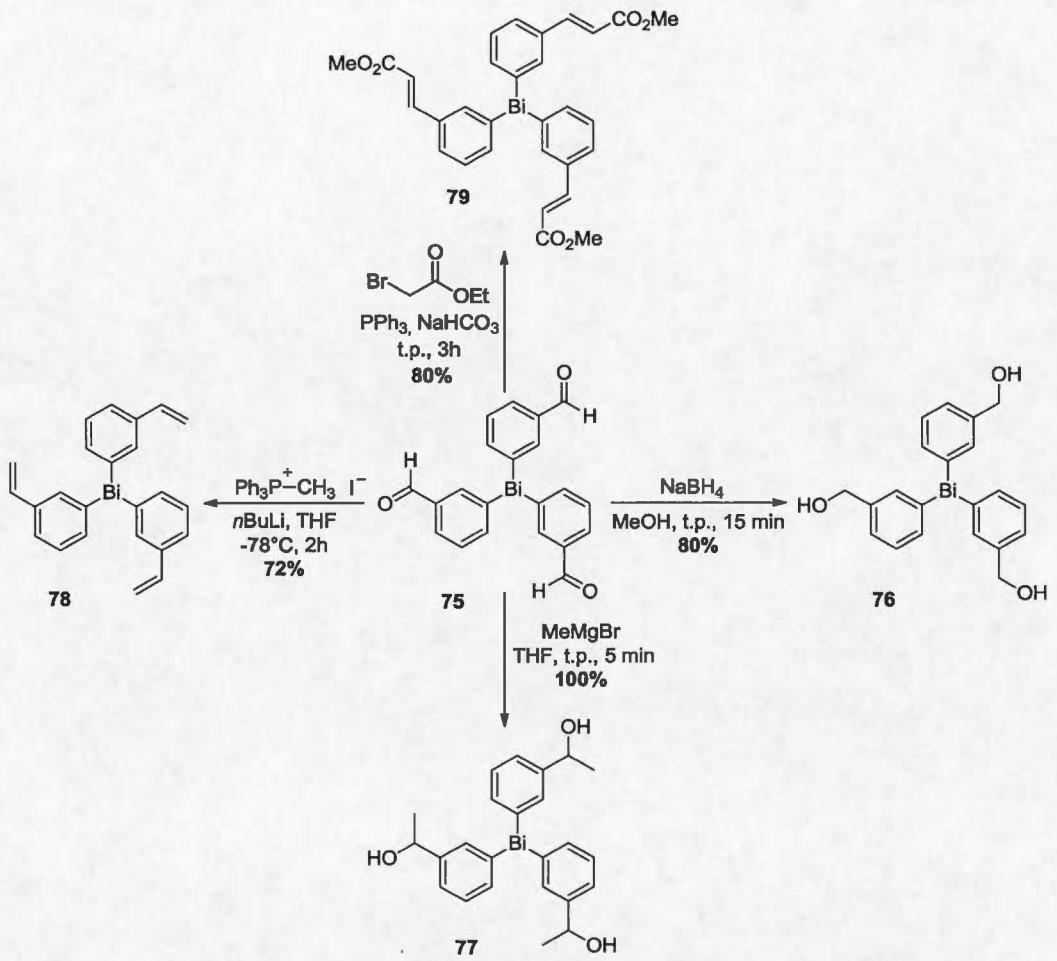


Schéma 26 : Fonctionnalisation du *tris*-formylphénylbismuth **75**

Tout d'abord, le *tris*-formylphénylbismuth **75** a été soumis à des conditions réductrices, permettant l'obtention du composé **76** portant un alcool primaire dans un rendement de 80%. Dans une réaction d'addition de bromure de méthyle magnésium sur l'aldéhyde **75**, l'alcool secondaire **77** a été formé de façon quantitative. Par la suite, une réaction de Wittig a été faite en présence de *n*-BuLi comme base et malgré la forte réactivité de ce composé, le vinyle terminal désiré **78** a été obtenu dans un bon rendement. Finalement, dans les conditions de Horner-Emmons-Wadsworth en

présence de triphénylphosphine, un ester α,β-insaturé **79** de géométrie *E* a été préparé à partir du composé **75** avec un rendement de 80%.

D'autres types de modifications ont par la suite été réalisées, notamment à partir de l'alcool secondaire 77 (**Schéma 27**). La réaction d'oxydation de Dess-Martin sur l'alcool secondaire **77** a conduit à la méthyle cétone 80 avec un rendement de 60%. Le risque majeur de cette réaction était la possibilité d'oxyder le bismuth car en effet, il a été démontré par Finet[35] que ce métal peut s'oxyder en présence d'oxydant iodé hypervalent. Or, dans ce cas-ci le produit désiré **80** a été observé dans un excellent rendement.

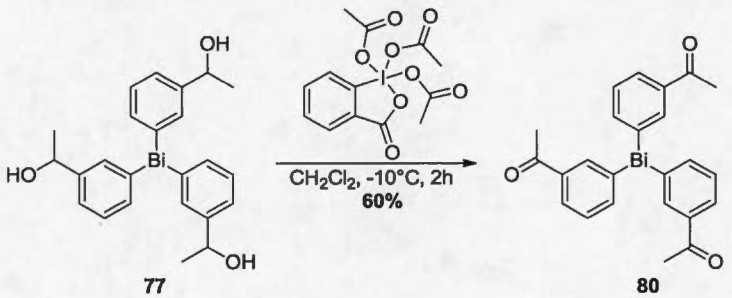


Schéma 27 : Synthèse du *tris*-méthylcétonephénylbismuth **80** à partir d'une réaction d'oxydation de Dess-Martin.

Par la suite, une réaction de métathèse croisée a été réalisée entre le vinyle terminal **78** et la méthyle vinyle cétone en utilisant le catalyseur de Grubbs II pour générer la cétone **81** correspondante avec un rendement de 69% (**Schéma 28**). La concentration du solvant est un point essentiel pour le succès de cette réaction. En effet, en solution plus concentrée, la réaction s'opère avec un rendement de seulement 20%.

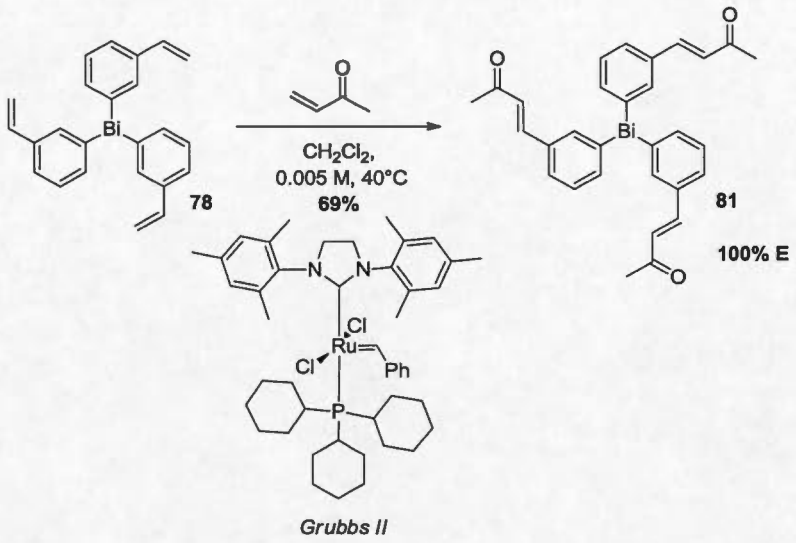


Schéma 28 : Synthèse du complexe **81** par réaction de métathèse croisée

Finalement, nous avons apporté deux dernières modifications à l'organobismuthane **64** portant un ester en position *para* (**Schéma 29**). Tout d'abord, une addition de méthyle Grignard mène à la formation du réactif **82** portant un alcool tertiaire. En milieu basique, l'ester méthylique **64** subit doucement une hydrolyse, ce qui permet d'obtenir l'acide carboxylique **83** sans dégradation de l'organométallique.

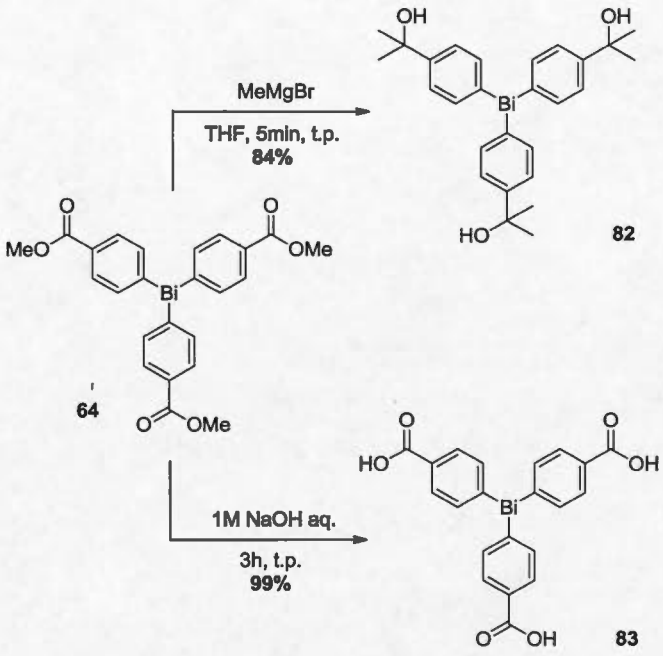


Schéma 29 : Fonctionnalisation du *tris*-(4-carbométhoxyphényl)bismuth **64**

La manipulation de groupements fonctionnels directement sur le bismuth n'a pas toujours été couronnée de succès durant nos études. En effet, de nombreuses modifications de groupements fonctionnels ou de synthèse d'organobismuthanes n'ont pas abouti au produit attendu. Tout d'abord, nous souhaitions déprotéger notre acétal tétrahydropyrane **66** en utilisant des conditions acides aqueuses (**Schéma 30**). Basé sur la réaction de déprotection de l'acétal **66**, nous avions de bonnes raisons de croire que cette réaction s'effectuerait sans problème. Toutefois, cette déprotection s'est avérée être plus difficile que prévu.

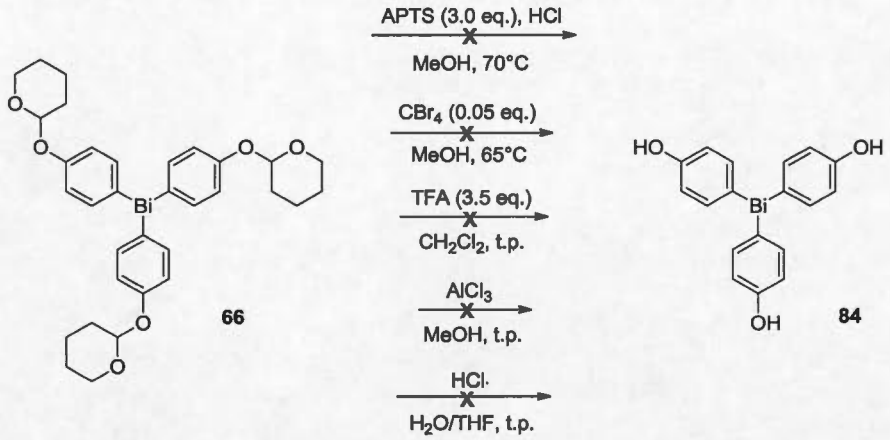


Schéma 30 : Essais de déprotections de l'acétal tétrahydropyrane **66**

Ainsi de nombreuses conditions opératoires ont été testées notamment avec $AlCl_3$ comme acide de Lewis, différents types d'acides comme HCl, APTS ou encore TFA et même une méthode de déprotection avec CBr_4 a été essayée. Ces conditions opératoires ont donné principalement le produit de départ ou des produits de dégradation.

Également, d'autres types de réaction ont été tentés à partir de notre réactif **75** portant un aldéhyde (**Schéma 31**).

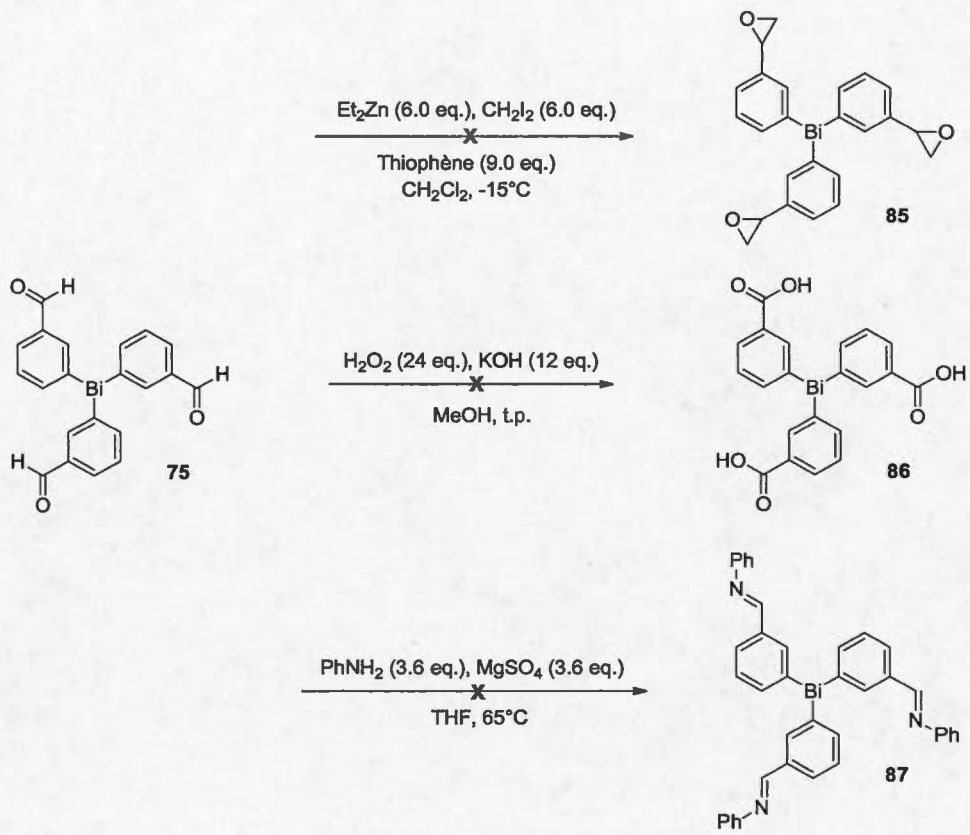


Schéma 31 : Essais de diverses réactions de manipulation du groupement aldéhyde sur le réactif organobismuthane **75**

Premièrement sur l'organobismuthane portant un aldéhyde, nous avons essayé de former un époxyde avec Et_2Zn et CH_2I_2 comme réactifs et ce, avec différents temps, températures et solvants mais le produit désiré n'a jamais été formé. De plus, une oxydation de cet aldéhyde **75** a été tentée en présence de H_2O_2 et KOH pour former l'acide carboxylique **86** correspondant, mais une nouvelle fois la réaction n'a pas fonctionné. Finalement, la dernière modification effectuée sur ce réactif organométallique **75** a été la formation d'une imine **87** en présence d'aniline. Dans ce cas-ci, uniquement de la dégradation a été observée.

Malgré quelques essais infructueux dans la fonctionnalisation de nos réactifs de bismuth, nous avons réussi à développer une large famille d'organobismuthanes hautement fonctionnalisés.

Contrairement à d'autres métaux comme le magnésium, il est possible de fonctionnaliser ces organobismuthanes avec des groupements réactifs tels que des aldéhydes, des alcools, des esters, etc. La préparation de ces composés organométalliques hautement fonctionnalisés a permis de tester leur intérêt dans un bon nombre de méthodologies de synthèse. La transférabilité, la diversité et la tolérance des groupements fonctionnels ont été étudiées.

0. 4. Formation de liens C–C par catalyse au palladium

Les réactions de couplage au palladium permettent la formation de liens C–C de manière contrôlée. De plus, elles peuvent être appliquées à la préparation de molécules complexes. Les catalyseurs de palladium démontrent une bonne tolérance à une large gamme de fonctionnalités. Les réactions de couplage de liens C–C les plus connues sont celles de Suzuki,[48a] Negishi,[48b] Stille[48c] et Kumada-Corriu[48d] qui emploient respectivement des réactifs de bore, de zinc, d'étain et de magnésium.

Pour ces premières études de couplage au palladium impliquant des organobismuthanes, nous avons sélectionné des 2-halo et 2-triflyl azines et diazines comme électrophiles. Ces espèces sont omniprésentes dans l'industrie pharmaceutique. En effet, les composés contenant ces hétérocycles azotés ont révélé des activités anti-microbiennes, anti-virales, anti-oxydantes et anti-tumorales.[49] Par conséquent, l'accès à des méthodes efficaces et générales qui permettent leur préparation est d'une importance capitale.[50]

Le couplage d'alkyles sp^3 sur ce type d'hétérocycles portant un halogène en position 2 est une méthode intéressante pour accéder aux dérivés alkylés correspondants.[51] Cependant, ce type de réaction est difficile et seulement quelques exemples isolés, avec des acides boroniques,[52] organozincs,[53] organomagnésiens[54] et organoétains[55] ont été rapportés. En effet, ces exemples souffrent d'un manque d'étendue de leur méthode, d'une faible tolérance aux groupements fonctionnels, nécessitent des conditions anhydres ou encore utilisent des catalyseurs onéreux pour palier l'élimination d'hydrures β (**Schéma 32**).

88 **89** **90**

Schéma 32 : Élimination d'hydrures β

Le premier couplage impliquant un trialkylbismuthane (**Schéma 33**) a été décrit en 2008 par Gagnon.[56] Dans cet exemple, un motif cyclopropyle a ainsi été greffé sur la 2-chloropyridine **91** par l'usage du tricyclopropylbismuth **92**. Le produit de couplage **93** a été obtenu avec un rendement de 65% en présence de tetrakis(triphénylphosphine)palladium comme catalyseur. Les conditions sont simples et ne requièrent aucun ligand ou additif complexe ou coûteux. Cependant, tout le potentiel de cette méthode n'a pas été établi dans cet article. En effet, les réactions d'alkylation ont été réalisées uniquement sur des pyridines, la tolérance aux groupements fonctionnels n'a pas été clairement démontrée et enfin, seulement le chlore a été utilisé en tant qu'halogène.

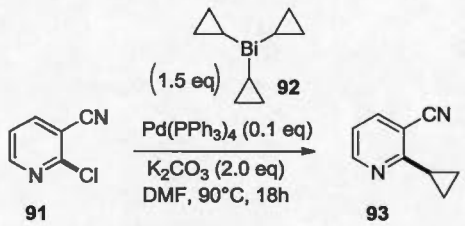


Schéma 33 : Réaction de couplage entre la 2-chloropyridine **91** et le tricyclopropylbismuth **92**

Au vu de la littérature, il n'existait pas de méthodes générales d'alkylation de 2-halo pyridines, pyrimidines, pyridazines et pyrazines. Par conséquent, nous avons pensé qu'il était opportun de développer une méthode efficace pour cette réaction de couplage (**Schéma 34**). Ce projet est issu d'un article, présenté au chapitre 1 et en annexes A et B.

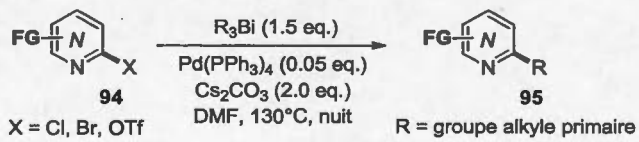


Schéma 34 : Synthèse de 2-alkylazines et diazines **95** par réaction de couplage avec des trialkylbismuthanes

Des conditions opératoires ont été développées de manière à ce qu'elles soient les plus simples possibles. En effet, cette méthode nécessite 5 mol% de $Pd(PPh_3)_4$, qui est un catalyseur commercialement disponible, et 2.0 équivalents de Cs_2CO_3 en tant que base. Aucuns catalyseurs ou ligands spéciaux n'ont été utilisés pour éviter l'élimination d'hydrures β. Dans notre méthode, 11 exemples ont été réalisés à partir de pyridines, pyrimidines, pyridazines et pyrazines avec des rendements allant jusqu'à 86%. Également, une bonne variété d'halogènes et de pseudo-halogènes sur l'électrophile **94** a été testée tel que chlore, brome et triflate. Finalement, la tolérance aux groupements fonctionnels a été démontrée, avec notamment des groupements de

type méthyle cétone, nitrile ou amine par exemple. Les résultats reliés à ce projet sont présentés en annexes A et B.

De plus, nous avons couplé des réactifs de type triarylbismuthane sur les 2-halo et 2-triflyl azines et diazines (**Schéma 35**) afin de mettre au point une approche d'intérêt pour l'accès aux hétérocyles arylés correspondants **98** en position 2. Ce projet est issu d'un article, présenté au chapitre 2 et en annexes C et D.

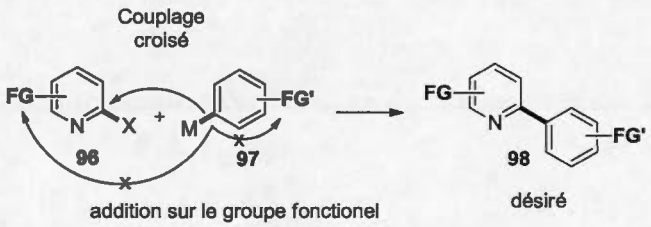


Schéma 35 : Réaction de couplage chimiosélective entre un organométallique **97** portant un groupement fonctionnel et une 2-halopyridine **96**

Quelques exemples de réactions de couplage sur des 2-haloazines et diazines ont été rapportés dans la littérature.[57, 58] Cependant, la plupart de ces méthodes démontrent une faible étendue, requièrent des réactifs sensibles à l'air et l'humidité ou encore des catalyseurs complexes. De plus, une tolérance limitée aux groupements fonctionnels est souvent observée, en particulier dans le cas de composés organométalliques sensibles tels que les organomagnésiens.[59] Bien que les organoétains soient plus tolérants vis-à-vis des groupements acides et électrophiles, leur grande toxicité combinée au fait qu'un seul aryle ne transfère, les rendent bien moins attrayants.[60] Le couplage des 2-haloazines et diazines avec des organozincs offre une bonne alternative pour la tolérance des groupements fonctionnels.[61] Cependant, leurs conditions de manipulation pourraient être problématique en cas d'application en chimie parallèle étant donné leur sensibilité à l'air et à l'humidité. De nos jours, les méthodes de Knochel[62, 63] et de Quéguiner[64] restent les méthodes les plus générales pour coupler des arylmétaux sur des 2-haloazines et diazines. Étant donné que ces

procédures utilisent des organomagnésiens, les groupements sensibles de type aldéhydes et cétones ne sont pas tolérés dans ces méthodes.

Après la découverte des réactions de couplage au palladium avec le triphénylbismuth par Barton et Finet en 1988,[65] d'autres groupes comme ceux de Rao,[66] Tanaka[67] et autres[68] ont développé ces réactions avec d'autres organobismuthanes. Cependant, le plein potentiel des triarylbismuthanes dans le transfert de groupements fonctionnels dans le couplage de 2-haloazines et diazines, n'a jamais été exploité. Dans le **Schéma 36**, le mécanisme d'action des organobismuthanes en réaction de couplage au palladium est présenté.

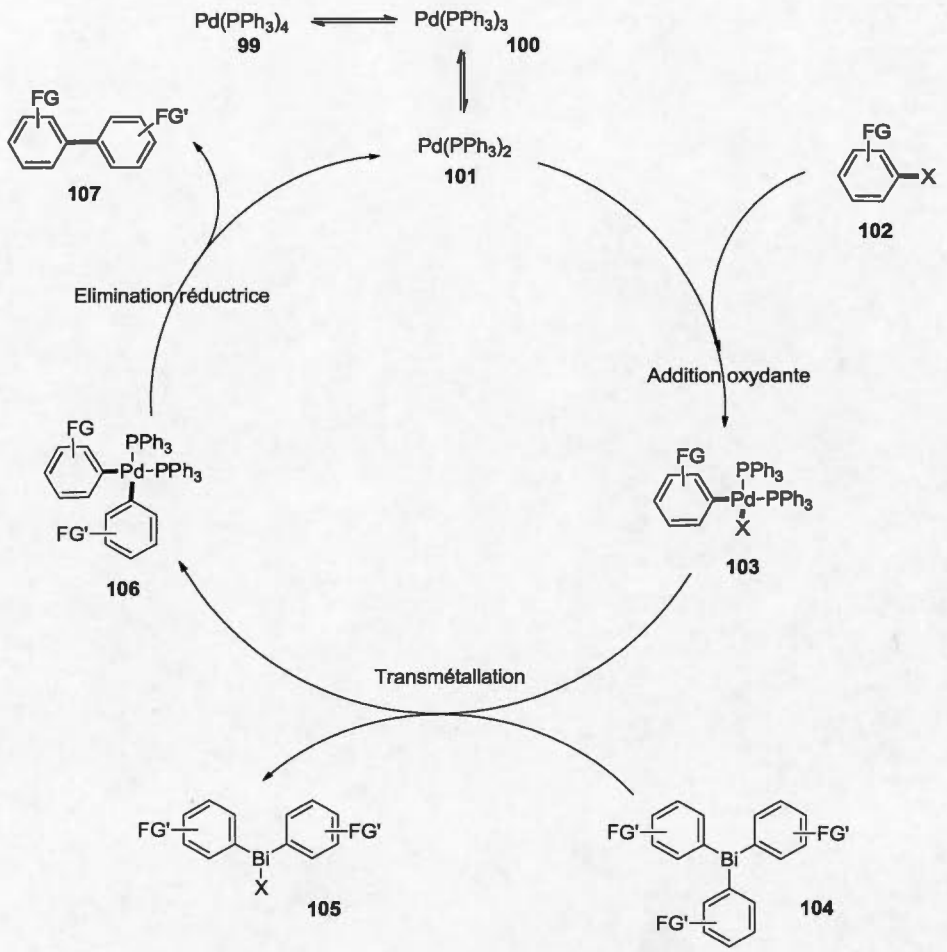


Schéma 36 : Cycle catalytique d'une réaction de couplage au palladium impliquant des organobismuthanes **104**

Les réactions de couplage au palladium sont caractérisées par 4 étapes caractéristiques. Le cycle catalytique débute par la formation de l'espèce réactive, $Pd(0)L_2$, qui provient de la perte de ligands de l'espèce stable de Pd(0) ou Pd(II). L'addition oxydante correspond à la réaction entre l'espèce $Pd(0)L_2$ et le réactif R_1X afin de former l'espèce organopalladée $R_1Pd(II)X$. Le réactif organométallique intervient dans l'étape de transmétallation afin de transformer l'espèce

organopalladée. L'étape finale consiste en la formation du produit de la réaction par élimination réductrice et en la régénération du palladium (0).

Après avoir établi la méthode pour le couplage des 2-haloazines et diazines avec des trialkylbismuthanes, nous avons repris et optimisé les conditions opératoires au couplage avec les triarylbismuthanes, c'est-à-dire avec 5 mol% de $Pd(PPh_3)_4$ et 2.0 équivalents de Cs_2CO_3 en tant que base (**Schéma 37**).

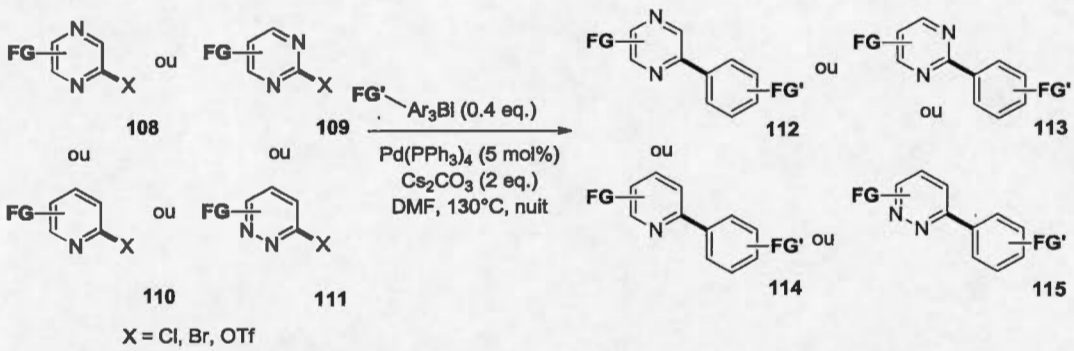


Schéma 37 : Couplage de triarylbismuthanes fonctionnalisés sur des 2-halo et 2-(triflyl)azines et diazines

De très nombreux exemples rapportés dans notre article ont démontré la diversité et la tolérance aux groupements fonctionnels de cette méthode. En effet, des groupements très sensibles comme des esters, aldéhydes, méthyle cétones ou encore alcools secondaires ont été testés et aucunes réactions secondaires n'ont été observées. Les résultats reliés à ce projet sont présentés en annexes C et D.

0. 5. Catalyse au cuivre

Les réactions de couplage au cuivre permettant la formation de liens C–C, C–N et C–O sont une longue histoire en chimie organique et ont été utilisées dans de nombreux procédés industriels.[69] Cependant, une limitation clé de ces méthodes est la nécessité de conditions opératoires difficiles (températures élevées et solvants

polaires) ainsi que l'utilisation de quantités stœchiométriques de catalyseur. Après d'importantes contributions antérieures,[70] une amélioration majeure est apparue en 2001 lorsque Buchwald a démontré que les ligands diamines permettent le couplage des halogénures d'aryles et d'amines, réaction connue sous le nom d'arylation de Goldberg, dans des conditions douces avec l'utilisation d'une base faible, d'un solvant non polaire, de température ambiante ainsi qu'une quantité catalytique de cuivre.[71] Ces nouvelles conditions opératoires ont considérablement augmenté l'utilisation des réactions de couplage au cuivre.[72] Ces méthodes sont robustes, utilisent des ligands simples et tolèrent une pléthore de groupements fonctionnels, ce qui les rendent extrêmement intéressantes pour la création de molécules à l'architecture complexe.

0. 5. 1. Formation de liens C–N

Après avoir développé des méthodes de formation de liens C–C par catalyse au palladium, la formation de liens C–N s'est imposée. En effet, nous avons rapporté la *N*-arylation d'indoles, d'indazoles, de pyrroles et de pyrazoles avec des organobismuthanes hautement fonctionnalisés. Ce projet est issu d'un article, présenté au chapitre 3 et en annexes E et F. Les azoles et diazoles sont des unités fréquemment utilisées en chimie médicinale pour projeter des pharmacophores clés le long de différents vecteurs à l'intérieur de la poche de liaison de la cible biologique.[73, 74] La *N*-arylation de ces composés azotés permet d'étudier de nouvelles interactions autour de l'inhibiteur[75] et de modifier ses propriétés biophysiques.[76] Également, les *N*-arylazoles et diazoles ont trouvé des applications dans la chimie des matériaux et des polymères.[77] En général, ces composés sont préparés via une *N*-arylation[78] par catalyse de métaux d'un N–H hétéroarène avec des halogénures d'aryles,[79] des acides boroniques[80] ou des réactifs de plomb.[81] Cependant, la toxicité des réactifs de plomb et les limitations des autres méthodes, comme de longs temps de réaction, des quantités super-stœchiométriques de catalyseur ou encore l'utilisation de ligands onéreux, restreignent ces méthodologies. De ce fait, le développement de nouvelles

approches qui permettent la synthèse d'arylazoles et diazoles fonctionnalisées sont souhaitables.

En 1988, Barton et Finet ont rapporté l'utilisation du triphénylbismuth-*bis*-trifluoroacétate dans l'arylation de l'indole **116** (**Schéma 38**).[82]

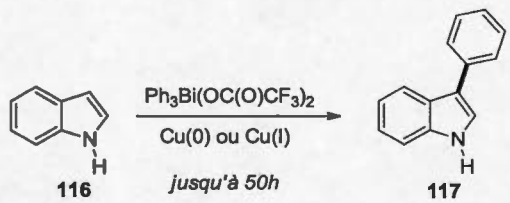


Schéma 38 : Arylation de l'indole **116** par la méthode de Barton et Finet avec du bismuth pentavalent

Cette méthode a été uniquement appliquée au transfert de groupements phényles non substitués et requiert l'utilisation de complexes de bismuth pentavalents, moins stables que leurs homologues trivalents. De plus dans la majorité des cas, l'arylation en position C3 a été observée, excepté lorsque cette position est bloquée par un groupe alkyle ou lorsqu'un ester est présent en position C2 de l'indole.

En 1996, Chan a publié une variation de protocole du l'article de Barton et Finet,[83] en utilisant des organobismuthanes de type trivalent pour la *N*-arylation de composés azotés (**Schéma 39**).[84]

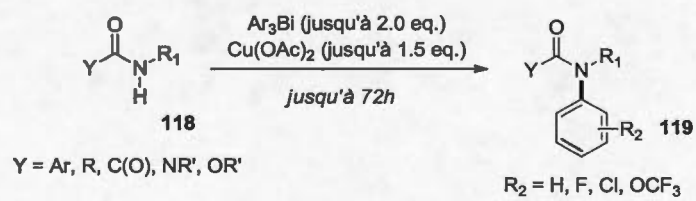


Schéma 39 : Arylation du composé **118** par la méthode de Chan avec du bismuth trivalent

Malgré l'utilité des méthodes de Barton et Chan, quelques limitations peuvent être soulevées. En effet, la quantité d'organobismuthane et de catalyseur nécessaires sont super-stœchiométriques et le temps de réaction peut aller jusqu'à 72h. De plus, cette approche n'a pas été appliquée aux indoles, indazoles, pyrazoles ou pyrroles, mais plutôt à des composés possédant un atome d'azote connecté à une fonction carbonyle. Finalement, la tolérance aux groupements fonctionnels n'a pas été démontrée car seulement des organobismuthanes classiques ont été couplés sur des substrats non fonctionnalisés.

Dans le **Schéma 40**, le mécanisme d'action des organobismuthanes en réaction de couplage au cuivre est présenté.

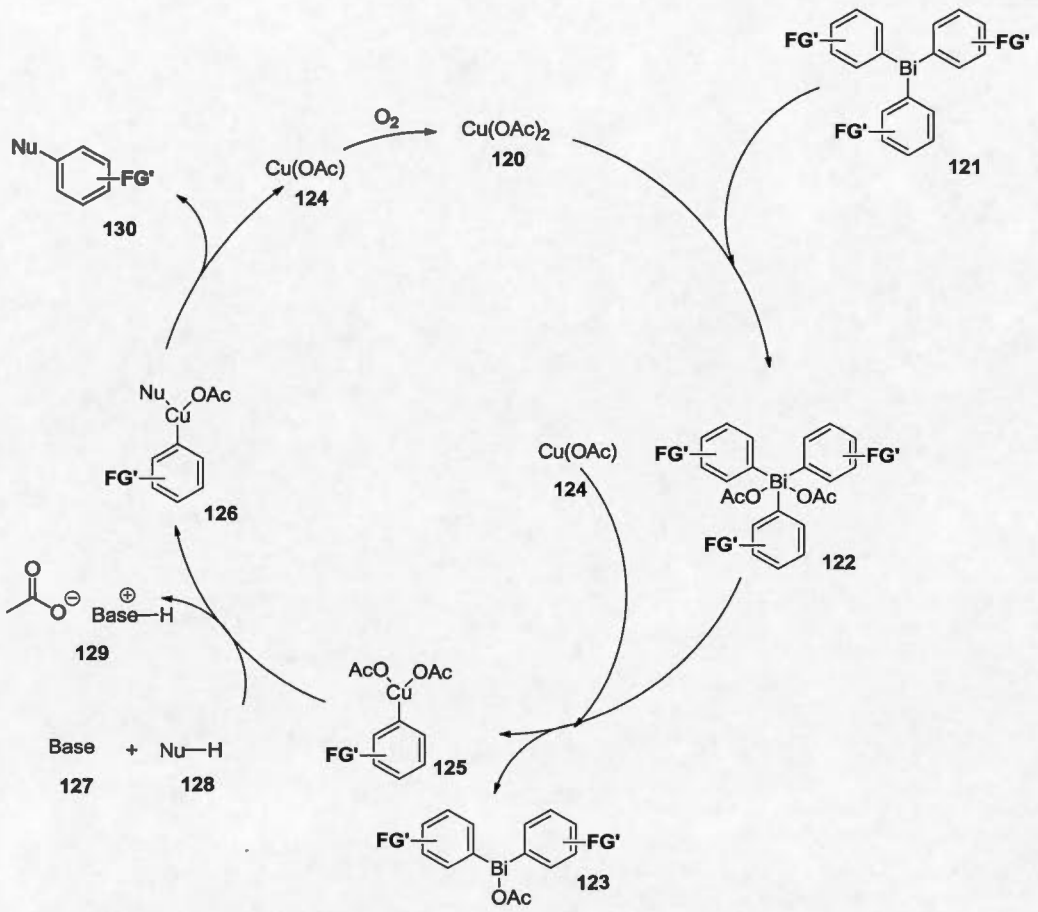


Schéma 40 : Cycle catalytique d'une réaction de couplage catalysée au cuivre impliquant des organobismuthanes **121**

La première méthode de *N*-arylation d'azoles et de diazoles **131** utilisant des organobismuthanes hautement fonctionnalisés et une quantité catalytique d'acétate de cuivre a été rapportée par notre groupe (**Schéma 41**). La présence d'oxygène dans la réaction permet de maintenir un taux catalytique en acétate de cuivre, possiblement en régénérant le catalyseur durant la réaction.

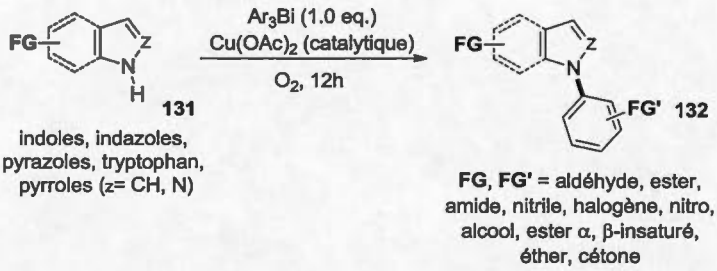


Schéma 41 : *N*-Arylation d'azoles et diazoles **131** avec des réactifs d'organobismuthanes trivalents hautement fonctionnalisés

Cette procédure permet d'accéder régiosélectivement au produit de *N*-arylation plutôt qu'au produit de C3-arylation et démontre une exceptionnelle tolérance aux groupements fonctionnels, que cela soit sur le substrat de départ ou sur le triarylbismuthane. En effet, des groupements très sensibles de type alcool primaire, cétone, aldéhyde, halogène, etc. sont tolérés dans ces conditions de réaction et aucunes réactions secondaires n'ont été observées malgré la haute fonctionnalisation des composés. Finalement, la méthode a été appliquée à la *N*-arylation de dérivés du tryptophane afin de former des produits de type *N*-aryltryptophane. Les résultats reliés à ce projet sont présentés en annexes E et F.

0. 5. 2. Formation de liens C–O

Après la création de liens C–C et C–N impliquant des organobismuthanes, la *O*-arylation de composés de type phénols ou 1,2-aminoalcools a été un des derniers sujets que nous avons exploré. Ce projet est issu d'un article, présenté au chapitre 4 et en annexes G et H. Étant donné l'efficacité de la méthode de *N*-arylation par catalyse au cuivre, il était raisonnable de penser que des réactions de *O*-arylation de composés oxygénés par catalyse au cuivre seraient tout aussi réalisables. En effet, un exemple de *N*-arylation d'azoles et de diazoles, qui a été abordée précédemment, a conduit au développement d'une nouvelle méthodologie par catalyse au cuivre (**Schéma 42**). Le premier exemple du **Schéma 42**, issu de notre article sur la *N*-arylation, démontre

qu'en présence d'un alcool primaire sur l'indole **133**, uniquement la *N*-arylation est observée. Or, lorsqu'il y a la présence d'une amine protégée par un Boc en β de l'alcool **135**, cette fois les produits de *N*- et la *O*-arylation sont obtenus. Incontestablement, l'amine joue un rôle crucial dans cette réaction. Ce cas particulier a donc été le déclencheur d'une nouvelle méthodologie qui est la *O*-arylation de 1,2-aminoalcools *N*-protégés.

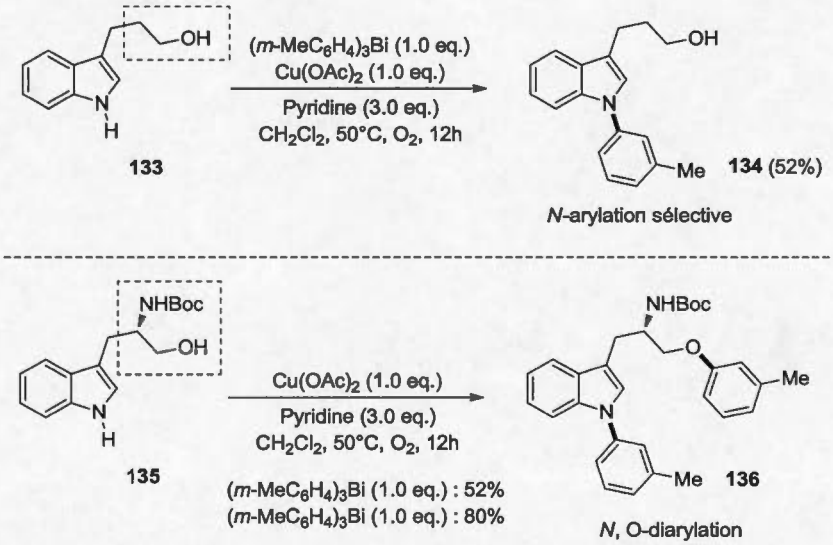


Schéma 42 : *N*- versus *O*-arylation du 3-(3-hydroxypropyl)-1*H*-indole **133** et du *N*-Boc-tryptophanol **135**

Les β-aryloxyamines sont fréquemment retrouvées dans les produits naturels et dans les composés d'intérêt pour la chimie médicinale. Ils peuvent être accessibles au travers de réactions de S_NAr entre des 1,2-aminoalcools et des halogénures d'aryles pauvres.[85] Également, ces composés peuvent être préparés à partir des mêmes précurseurs, mais par la réaction de Mitsunobu[86] ou via une réaction de S_N2 sur des mésylates ou tosylates correspondants.[87] Malgré que ces méthodes soient très courantes dans l'industrie pharmaceutique, elles souffrent de quelques limitations. En effet, elles nécessitent la présence de groupements attracteurs d'électrons sur

l'aromatique (S_NAr), la dérivatisation de l'alcool dans le cas de la S_N2 ou alors elles conduisent à la formation de produits secondaires, ce qui peut compliquer l'isolation du produit désiré (triphénylphosphine et urée dans la réaction de Mitsunobu).

La *O*-arylation de 1,2-aminoalcools par catalyse au cuivre utilisant des halogénures d'aryles a été illustrée par les travaux novateurs de Buchwald[88] et Evano[89] **(Schéma 43)** qui constitue une stratégie efficace pour la synthèse des β-aryloxyamines.[90-92]

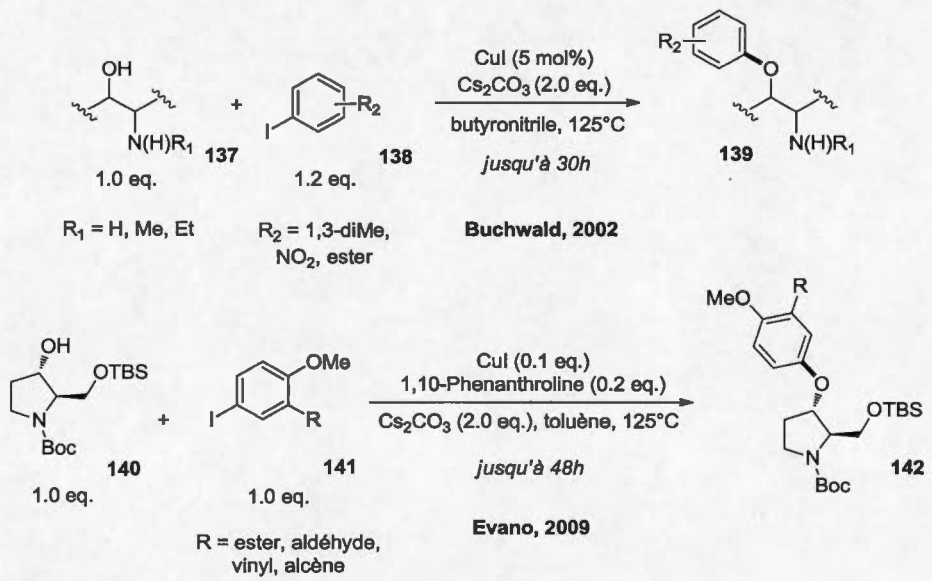


Schéma 43 : Méthodes pour la *O*-arylation des 1,2-aminoalcools par catalyse au cuivre décrites par Buchwald et Evano

Ces méthodes tolèrent un grand nombre de groupements fonctionnels et ne nécessitent pas de réactifs organométalliques. Cependant, les longs temps de réaction et la haute température de chauffage peuvent être un frein suivant la molécule de départ utilisée. De manière surprenante, la *O*-arylation des 1,2-aminoalcools utilisant des composés organométalliques a été beaucoup moins étudiée et le seul exemple utilisant cette technique a été développé par Mukaiyama et implique le fluorure de tetraphénylbismuth comme source d'aryle **(Schéma 44)**.[93]

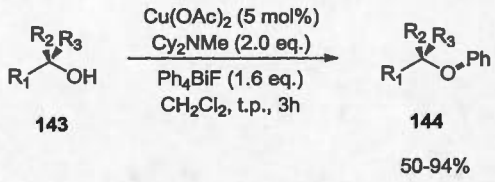


Schéma 44 : *O*-Arylation de 1,2-aminoalcools en présence de Ph_4BiF

Le développement d'une nouvelle procédure de *O*-arylation de 1,2-aminoalcools s'appuie sur les conditions opératoires que nous avons déterminé dans le projet de *N*-arylation d'azoles et de diazoles, étant donné le lien exposé précédemment entre ces deux projets (**Schéma 45**).

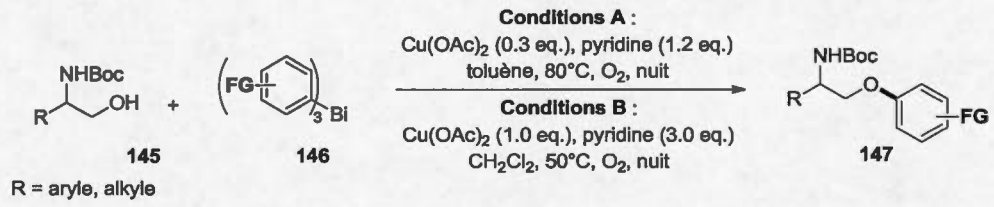


Schéma 45 : *O*-Arylation de 1,2-aminoalcools **145** utilisant des organobismuthanes fonctionnalisés **146**

Les conditions opératoires nécessitent une quantité catalytique d'acétate de cuivre qui est possible grâce à la présence d'oxygène dans la réaction et 1.2 à 3.0 équivalents de pyridine suivant les conditions utilisées. En plus de la table de substrats que nous avons réalisée pour démontrer l'étendue de la méthode, de nombreuses expériences ont été effectuées afin de déterminer par quel mécanisme l'amine dirige la *O*-arylation de l'aminoalcool. Après de nombreux tests de réactivité, nous avons déterminé que la présence de l'amine en β de l'alcool permettait de diminuer le pK_a de celui-ci afin qu'il puisse réagir avec l'oganobismuthane **146**. Les résultats reliés à ce projet sont présentés en annexes G et H.

La dernière méthodologie développée pour la formation de liens C–O par catalyse au cuivre est la *O*-arylation de phénols avec l'utilisation des organobismuthanes. Cet

article publié par notre groupe en 2014 ne sera pas rapporté dans cette thèse, mais il est important d'aborder cette technique très efficace dans la synthèse des diaryles éthers fonctionnalisés.

Les diaryles éthers sont des composés que l'on retrouve aisément dans la nature[94] et dans les molécules d'intérêt pour la chimie médicinale.[95] Ce motif a aussi été identifié dans des peptides naturels comme la vancomycine, compléstatine, teicoplanine et eurypamide.[96] Dû à leurs diverses activités biologiques, la synthèse des diaryles éthers est de la plus grande importance. Pour être applicable à la synthèse de produits naturels, les méthodes de synthèse des diaryles éthers doivent tolérer une gamme importante de groupements fonctionnels. De plus, pour trouver une large étendue en chimie médicinale, ces protocoles doivent opérer sous de simples conditions opératoires afin d'être applicables en chimie parallèle et ne doivent pas nécessiter l'utilisation de ligands ou catalyseurs complexes ou coûteux.[97] La réaction d'Ullmann, qui consiste au couplage d'un phénol avec un halogénure d'aryle par catalyse au cuivre, est la première méthode rapportée pour la synthèse des diaryles éthers (**Schéma 46**).[98]

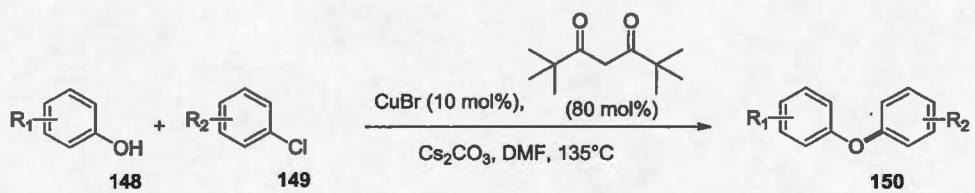
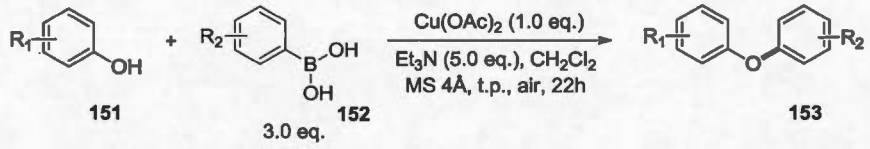


Schéma 46 : Arylation du phénol **148** avec un halogénure d'aryle **149** par la méthode d'Ullmann

Cependant, la nécessité d'utiliser des hautes températures de réaction empêche son emploi dans la synthèse de molécules complexes. La solution apportée par Evans, Chan et Lam, et qui consiste en un couplage entre un acide boronique et un phénol, a permis de résoudre le problème de synthèse des diaryles éthers (**Schéma 47**).[99, 100]



R_1, R_2 = attracteur, donneur d'électrons

Schéma 47 : Arylation de phénol **151** avec un acide boronique **152** par la méthode d'Evans, Chan et Lam

Malgré le fait que cette procédure soit plutôt générale, l'excès d'acide boronique est souvent nécessaire afin d'obtenir de bons rendements. Récemment, l'introduction de ligands complexant de cuivre par Buchwald a permis l'utilisation d'une quantité catalytique de cuivre pour la réaction d'Ullmann.[101] La *O*-arylation de phénols peut aussi être réalisée en utilisant des aryliodoniums, tel que rapportée par Olofsson.[102] Cependant, dans ce cas, une base forte est généralement utilisée pour promouvoir la réaction. L'utilisation des composés organométalliques reste une stratégie attrayante pour la synthèse des diaryles éthers fonctionnalisés.[103] Cette approche n'a pas été uniquement mise en pratique avec les acides boroniques,[99, 100] mais aussi avec les trifluoroborate de potassium,[104] les organoplombs[105] et les organoétains.[106] Dans les années 80, Barton a rapporté l'utilisation du triphénylbismuth diacétate dans la *O*-arylation de phénols.[107] Or, ces études qui reposent sur une préformation du bismuth pentavalent, n'ont pas démontré le tolérance de la méthode aux groupements fonctionnels et impliquent uniquement le transfert de groupements aryles non substitués. Après la publication de ce travail de pionnier, quelques exemples isolés de *O*-arylation de phénols utilisant des organobismuthanes trivalents ont été rapportés.[108] Cependant, il n'existe qu'un seul article illustrant une méthode relativement complète de *O*-arylation de phénols avec les organobismuthanes, mais celle-ci implique du $PhI(OAc)_2$ comme co-oxydant, ce qui constitue une limitation importante.[109]

Au vu de la littérature, il était intéressant de développer une méthode efficace avec des conditions opératoires simples afin de pouvoir proposer une solution concurrentielle aux méthodes existantes (**Schéma 48**).

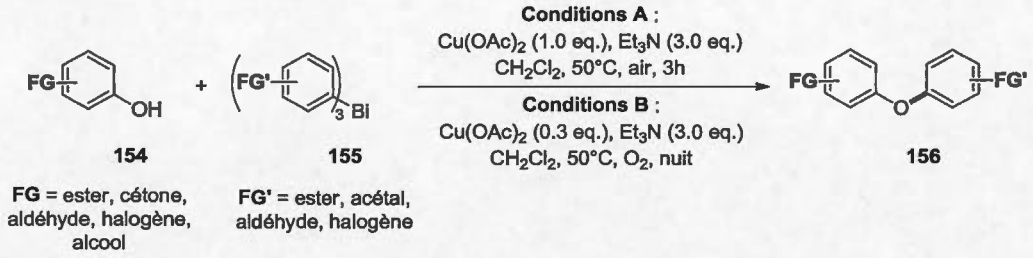


Schéma 48 : *O*-Arylation de phénols fonctionnalisés **154** avec des triarylbismuthanes substitués **155**

La méthode que nous avons développée est générale car, grâce à des conditions douces de réaction et une très bonne tolérance aux groupements fonctionnels, elle peut être adaptée à de nombreux composés complexes tels que des produits naturels. En effet, des groupements sensibles de type aldéhyde, cétone ou alcool ont été testés et des rendements allant jusqu'à 98% ont été observés. De plus, cette approche a été comparée avec celle d'Evans, Chan et Lam afin de pouvoir juger de son efficacité (**Schéma 49**).

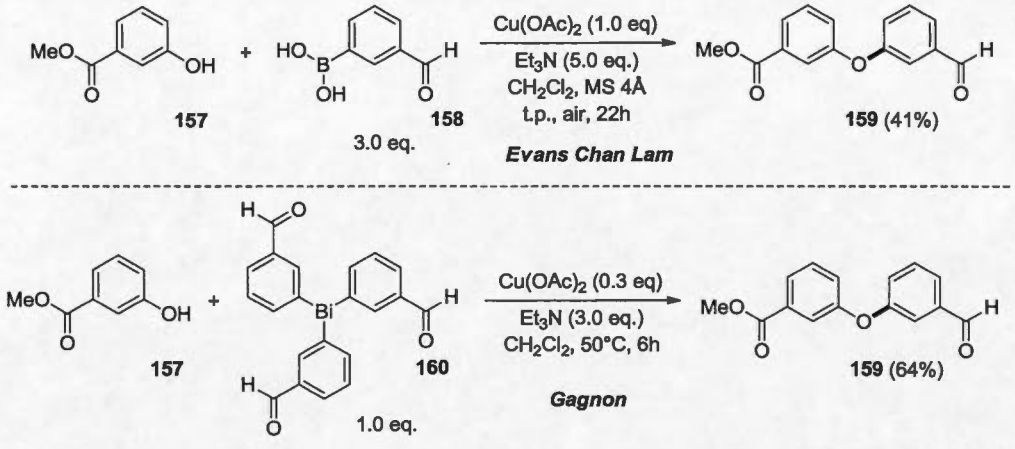


Schéma 49 : Comparaison de *O*-arylation du 3-hydroxy benzoate de méthyle **157** avec l'acide boronique **158** et l'organobismuthane **160**

Avec les conditions classiques d'Evans, Chan et Lam trouvées dans la littérature,[99a] le diaryle éther **159** a été obtenu avec un rendement de 41% après 22h de réaction à température ambiante. Le même produit a été synthétisé avec un rendement de 64% après 6h de réaction en utilisant l'organobismuthane **160** et 0.3 équivalents d'acétate de cuivre. En utilisant les conditions développées avec l'organobismuthane dans la réaction avec l'acide boronique, le produit **159** a été obtenu avec seulement 14% de rendement.

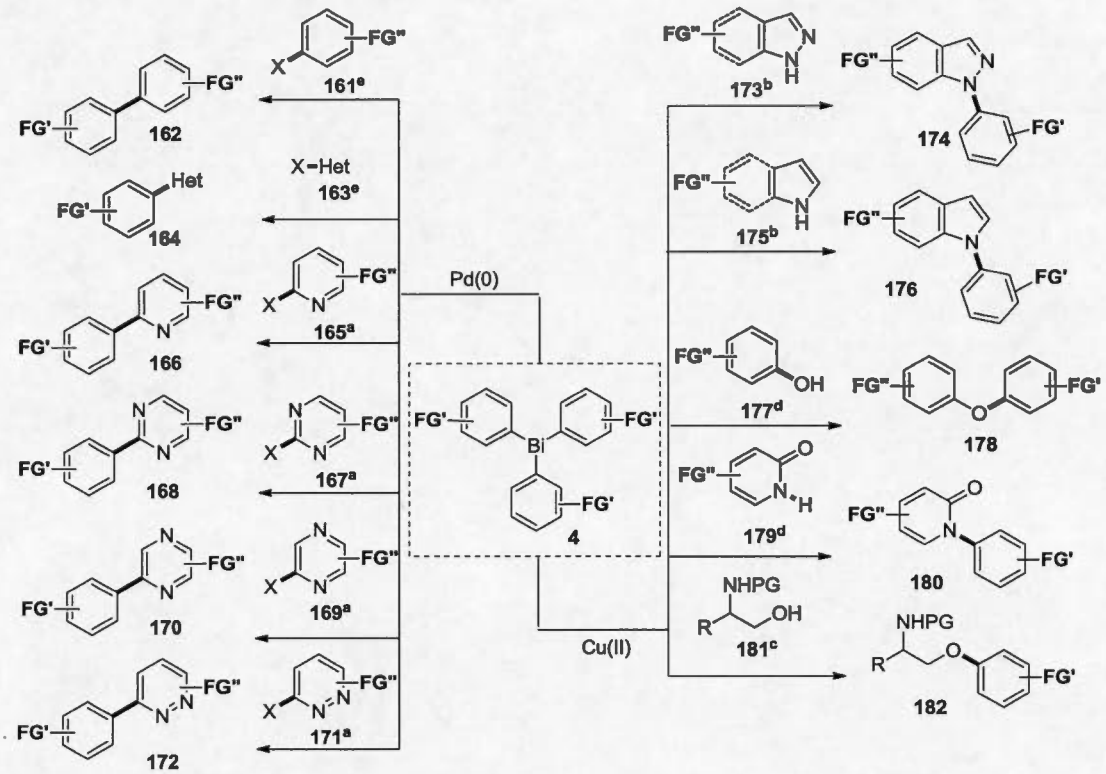
0. 6. Étendue des méthodes d'arylation

La préparation de molécules complexes repose sur notre capacité à former de nouvelles liaisons de manière contrôlée. Afin d'y parvenir, l'accès à des méthodes efficaces qui permettent la création de nouvelles liaisons en présence de groupements fonctionnels est essentiel. De plus, ces méthodes doivent, idéalement, être simples et robustes pour être appliquées en chimie parallèle permettant ainsi la préparation de banques de composés intéressants du point de vue de la chimie médicinale.

Les réactifs organométalliques ont révolutionné le domaine de la chimie organique en facilitant la formation de liens difficiles d'accès. Cependant, certains de ces réactifs souffrent d'importantes limitations comme une sensibilité à l'air et l'humidité, de pyrophoricité, d'une faible stabilité et d'une faible compatibilité avec des groupements fonctionnels. Récemment, les travaux de Knochel et d'autres sur la préparation de composés organométalliques fonctionnalisés ont contribué à résoudre certains problèmes reliés à ces réactifs tel que la tolérance aux groupements fonctionnels, la toxicité, la mise en œuvre des réactions, etc.

Depuis quelques années, les organobismuthanes démontrent qu'ils sont une classe de réactifs organométalliques à part entière. Ces réactifs peuvent être préparés à partir des sels de bismuth non toxiques et peu coûteux ou alors par la méthode de Grignard tel qu'abordée précédemment. Les triarylbismuthanes sont particulièrement intéressants car ils sont stables à l'air et à l'humidité. En effet, ils peuvent être purifiés par chromatographie sur colonne ou par cristallisation et être stockés sur la paillasse. En raison de la faible force de la liaison bismuth-carbone, les réactifs organobismuthanes sont remarquablement tolérants à de nombreux groupes fonctionnels. Leur réactivité est déterminée par l'état d'oxydation du bismuth, soit le bismuth(III) trivalent qui réagit en tant que réactif nucléophile ou soit le bismuth(V) pentavalent qui se comporte comme une espèce électrophile. Dans les années 1980, Barton et Finet ont exploité ce double mode de réactivité pour développer une série de réactions métalo-catalysées à base d'organobismuthanes. Plus récemment, les travaux de Condon et Rao sur ces composés organométalliques particuliers ont contribué à étendre l'application de cette classe de réactifs en synthèse organique. Après avoir rapporté de nombreuses méthodes de formation de liens C–C, C–N et C–O impliquant les organobismuthanes, une étendue de ces méthodologies et de la fonctionnalisation des complexes a été envisagée dans notre dernier projet. Il est issu d'un article en cours d'écriture, présenté au chapitre et en annexes I et J. Ces différentes approches que nous avons développées, ont permis le transfert de groupes

aryles fonctionnalisés sur différents types de substrats, comme des arènes **161** et des hétéroarènes **163**, des pyridines **165**, des pyrimidines **167**, des pyrazines **169** et des pyridazines **171**, des indazoles et des pyrazoles **173**, des indoles et des pyroles **175**, des phénols **177**, des pyridones **179** et finalement sur des 1,2-aminoalcools **181** afin d'accéder à une grande gamme de produits médicinalement pertinents (**Schéma 50**).



[a]P. Petiot, A. Gagnon, *Eur. J. Org. Chem.*, **2013**, 5282;
[b]P. Petiot, J. Dansereau, A. Gagnon, *RSC Adv.* **2014**, 22255
[c]P. Petiot, J. Dansereau, M. Hébert, I. Khene, T. Ahmad, S. Samaali, M. Leroy, F. Pinsonneault, C. Legault, A. Gagnon, *Org. Biomol. Chem.* **2015**, *13*, 1322;
[d]C. Crifar, P. Petiot, T. Ahmad, A. Gagnon, *Chem. Eur. J.* **2014**, *20*, 2755;
[e]Article en cours d'écriture

Schéma 50 : Triarylbismuthanes dans des réactions d'arylation : synthèse de composés hautement fonctionnalisés et médicinalement pertinents

Dans cet article en préparation, la synthèse d'organobismuthanes a été développée, c'est-à-dire que des groupements de type alcools (primaire, secondaire et tertiaire), cétone et ester α,β-insaturé, cétone, aldéhyde et vinyle terminal ont été greffés sur des triarylbismuthanes. Ces complexes hautement fonctionnalisés ont été, par la suite, transférés sur tous les types de substrats présentés auparavant dans cette thèse. Les résultats reliés à ce projet sont présentés en annexes I et J.

CHAPITRE I

RÉACTION DE COUPLAGE ENTRE DES TRIALKYLBISMUTHANES ET DES 2-HALOAZINES ET DIAZINES CATALYSÉE AU PALLADIUM

1. 1. Introduction

Les 2-haloazines et diazines sont des espèces très convoitées dans la chimie médicinale. En effet, ces composés ont révélé des activités anti-microbiennes, anti-virales, anti-oxydantes et anti-tumorales. Par conséquent, l'accès à des méthodes efficaces et générales qui permettent leur préparation est d'une importance capitale. De plus, le couplage d'alkyles sp^3 sur ce type de substrats portant un halogène en position 2 est une méthode intéressante pour accéder aux dérivés alkylés correspondants. Or à ce jour, il n'existe pas de méthodes complètes et générales pour la préparation de ce genre de composés car bien souvent, la réaction secondaire d'élimination d'hydrure β est observée. La méthode de couplage présentée dans les annexes A et B, démontre que des conditions simples de réaction peuvent être développées, avec, par exemple, un catalyseur peu coûteux et commercial, l'absence de ligand afin d'éviter une possible élimination d'hydrure β et être totalement compatibles avec des groupements fonctionnels.

1. 2. Informations supplémentaires

L'article issu de ces travaux est présenté à l'annexe A. Les informations supplémentaires, contenant les protocoles expérimentaux ainsi que les caractérisations et spectres RMN, sont présentés à l'annexe B.

1. 3. Conclusion

En conclusion, une procédure efficace et générale pour le couplage d'alkyles sur des 2-haloazines et diazines a été développée à partir de trialkylbismuthanes. En effet, cette méthodologie opère sous de simples conditions de réaction avec l'utilisation d'un catalyseur simple. De nombreux groupements fonctionnels sont tolérés et les composés synthétisés ont une importante valeur en chimie médicinale.

CHAPITRE II

RÉACTION DE COUPLAGE ENTRE DES TRIARYLBISMUTHANES AVEC DES 2-HALO(ou 2-TRIFLYL) AZINES ET DIAZINES CATALYSÉE AU PALLADIUM

2. 1. Introduction

Des réactifs organométalliques de type triarylbismuthanes ont été couplés sur les 2-halo et 2-triflyl azines et diazines afin de constituer une approche d'intérêt, pour l'accès à ces hétérocyles arylés en position 2 en chimie médicinale. De nombreuses méthodes existantes permettent de réaliser ce couplage. Or la plupart de ces méthodes comportent soit des difficultés de mise en œuvre notamment avec les organozincs soit une incompatibilité de groupements fonctionnels avec les organomagnésiens par exemple. La méthode de couplage proposée ici, démontre que des conditions simples de réaction peuvent être développées, avec, par exemple, un catalyseur peu coûteux et commercial et être totalement compatibles avec des groupements fonctionnels sensibles.

2. 2. Informations supplémentaires

L'article issu de ces travaux est présenté à l'annexe C. Les informations supplémentaires, contenant les protocoles expérimentaux ainsi que les caractérisations et spectres RMN, sont présentés à l'annexe D.

2. 3. Conclusion

Une nouvelle méthode d'arylation a été proposée à partir de triaryl- et tri-hétéroarylbismuthanes fonctionnalisés sur des 2-halo- et 2-triflylazines et diazines. Cette procédure utilise des organobismuthanes stables et opère sous de simples conditions, ce qui mène à l'obtention des produits désirés avec de bons à excellents rendements. De plus, les trois groupes aryles sur le bismuth sont transférés dans cette réaction, ce qui permet une économie d'atomes. Pour la première fois dans cet article, il a été démontré que la manipulation de groupement fonctionnel directement sur l'organométallique, afin de transformer un acétal en aldéhyde, est efficace.

CHAPITRE III

N-ARYLATION D'AZOLES ET DE DIAZOLES CATALYSÉE AU CUIVRE IMPLIQUANT DES ORGANOBISMUTHANES HAUTEMENT FONCTIONNALISÉS

3. 1. Introduction

Tout comme les azines et diazines, les azoles et diazoles sont des unités fréquemment utilisées non seulement en chimie médicinale, mais également dans la chimie des matériaux et polymères. Les méthodes existantes pour la *N*-arylation de ces composés souffrent de nombreuses limitations comme des temps de réaction extrêmement longs, l'usage de réactifs toxiques ou des quantités super-stœchiométriques de catalyseur. Il était alors nécessaire de développer une méthode simple et efficace à partir des triarylbismuthanes afin de générer les molécules les plus fonctionnalisées possibles. Également, l'arylation de dérivés de tryptophane a été proposée dans le but d'être applicables en chimie médicinale.

3. 2. Informations supplémentaires

L'article issu de ces travaux est présenté à l'annexe E. Les informations supplémentaires, contenant les protocoles expérimentaux ainsi que les caractérisations et spectres RMN, sont présentés à l'annexe F.

3. 3. Conclusion

Pour résumer, une nouvelle méthodologie de *N*-arylation d'indoles, d'indazoles, de pyrroles et de pyrazoles a été proposée à partir d'organobismuthanes hautement fonctionnalisés. La transformation opère avec une quantité catalytique de cuivre et tolère une exceptionnelle diversité de groupements fonctionnels sur les deux partenaires de couplage afin d'accéder aux azoles et diazoles fonctionnalisées. L'utilisation de cette méthode pour l'arylation de dérivés du tryptophane est le point de départ d'un nouveau projet pour l'arylation d'aminoacides et de peptides contenant des unités tryptophanes.

CHAPITRE IV

O-ARYLATION DE 1,2-AMINOALCOOLS *N*-PROTÉGÉS CATALYSÉE AU CUIVRE IMPLIQUANT DES ORGANOBISMUTHANES HAUTEMENT FONCTIONNALISÉS

4. 1. Introduction

Les β-aryloxyamines sont fréquemment retrouvées dans les produits naturels et dans les composés d'intérêt pour la chimie médicinale. Ces composés peuvent être accessibles à partir de différentes méthodes comme des réactions de S_NAr, Mitsunobu ou via une réaction de S_N2 sur des 1,2-aminoalcools et des halogénures d'aryles. Malgré que ces méthodes soient très courantes dans l'industrie pharmaceutique, elles souffrent de quelques limitations comme la nécessité d'avoir des groupements attracteurs ou la formation de produits secondaires. Or, la réaction d'arylation des 1,2-aminoalcools *N*-protégés a été très peu étudiée à partir d'organométalliques comme agents de couplage. La seule méthode rapportée utilisant un réactif métallique est l'approche utilisant du fluorure de tetraphénylbismuth comme source arylante. De ce fait, le développement d'une nouvelle méthodologie de *O*-arylation de 1,2-aminoalcools à partir de bismuth trivalent, bien plus stable que son homologue pentavalent, a été réalisée afin de proposer un protocole efficace avec peu de limitations.

4. 2. Informations supplémentaires

L'article issu de ces travaux est présenté à l'annexe G. Les informations supplémentaires, contenant les protocoles expérimentaux ainsi que les caractérisations et spectres RMN, sont présentés à l'annexe H.

4. 3. Conclusion

En conclusion, une *O*-arylation de 1,2-aminoalcools catalysée au cuivre à partir d'organobismuthanes fonctionnalisés a été proposée. La réaction opère avec une quantité catalytique de cuivre et tolère une bonne variété de groupements fonctionnels sur l'organobismuthane afin d'accéder aux β-aryloxyamines fonctionnalisées correspondantes. Différents groupes protecteurs sur l'amine dans cette réaction d'arylation peuvent être utilisés comme le BOC, Cbz, Ac et Ts. Finalement, il a été démontré que la présence d'un groupement amine en β d'un alcool permet une augmentation de sa réactivité probablement dû à un effet inductif.

CHAPITRE V

SYNTHÈSE D'ORGANOBISMUTHANES HAUTEMENT FONCTIONNALISÉS PAR MANIPULATION DE GROUPEMENTS FONCTIONNELS ET UTILISATION DANS DES RÉACTIONS D'ARYLATION

5. 1. Introduction

Les méthodologies proposées jusqu'à présent avec les organobismuthanes ont pour objectif la création de nouveaux liens C–C, C–N et C–O en présence de groupements fonctionnels sans que cela n'altère leurs efficacités. Il est primordial aujourd'hui de développer des méthodes efficaces et simples qui respectent tous types de fonctionnalisations afin qu'elles puissent être appliquées à plus grande échelle en chimie médicinale. Dans ce dernier projet, la fonctionnalisation des organobismuthanes a été poussée à son paroxysme et ils ont été couplés sur tous les types de substrats présentés dans cette thèse.

5. 2. Informations supplémentaires

L'article en préparation issu de ces travaux est présenté à l'annexe I. Les informations supplémentaires, contenant les protocoles expérimentaux ainsi que les caractérisations et spectres RMN obtenus jusqu'alors, sont présentés à l'annexe J.

5. 3. Conclusion

Le résumé et l'extension des travaux réalisés depuis le début de cette thèse sont ici l'objet d'un article en cours d'écriture. L'application des organobismuthanes les plus fonctionnalisés possibles, aux arènes et aux hétéroarènes, aux azines et diazines, aux indazoles et aux pyrazoles, aux indoles et aux pyroles, aux phénols et aux pyridones et finalement aux 1,2-aminoalcools, donne accès à une grande gamme de produits médicinalement pertinents.

CONCLUSION

En conclusion, la synthèse d'organométalliques fonctionnalisés à base de bismuth par manipulation de groupements fonctionnels a été réalisée. De façon surprenante, le lien C–Bi tolère de nombreuses conditions de réaction telle que des conditions acides, basiques, oxydatives, réductrices, etc., grâce à la faible réactivité de ce lien carbone-métal. Des groupements de type alcool, cétone, aldéhyde, ester, vinyle et autres ont pu être synthétisés de manière efficace sans observer de dégradation de l'organométallique ni de réactions secondaires. Ces nouveaux organométalliques de choix ont été appliqués dans des réactions de couplage afin de démontrer l'étendue de leurs possibilités. En effet, nous avons développé de nouvelles méthodologies d'arylation, à partir d'organobismuthanes pour la création de nouveaux liens C–C, C–N et C–O. De plus, il a été possible de synthétiser de nombreuses unités fréquemment retrouvées dans des composés d'importance en chimie médicinale de type biaryles, hétéroaryles arylés, 2-arylazines et diazines, *N*-arylindazoles et pyrazoles, *N*-arylindoles et pyrroles, diaryles éthers, *N*-arylpyridones et des β-aryloxyamines. Les réactifs de bismuth, en raison de leur faible réactivité relative, ont permis d'élaborer des réactions simples d'application, utilisant des réactifs commerciaux abordables et tolérant une exceptionnelle diversité de groupements fonctionnels, que ce soit sur l'organométallique lui-même ou sur le substrat. Tous ces travaux mettent en lumière l'importance des organobismuthanes en chimie organique et leur exceptionnelle utilité dans les réactions de couplage au palladium ou au cuivre.

ANNEXE A

"PALLADIUM-CATALALYZED CROSS-COUPLING REACTION OF TRIALKYLBISMUTHINES WITH 2-HALOZINES AND DIAZINES" ARTICLE

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Titre : Palladium-Catalyzed Cross-Coupling Reaction of Trialkylbismuthines with 2-Haloazines and Diazines

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PALLADIUM-CATALYZED CROSS-COUPLING REACTION OF TRIALKYLBISMUTHINES WITH 2-HALOAZINES AND DIAZINES†

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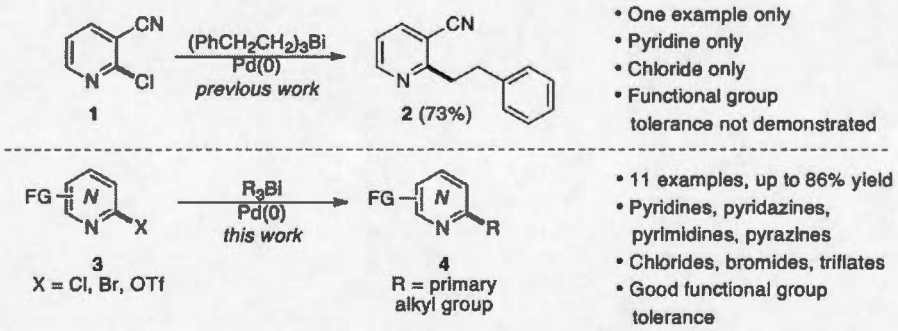
† This contribution is dedicated to Prof. Victor Snieckus on the occasion of his 77th birthday and for his outstanding contribution to organometallic chemistry.

Abstract – An efficient method for the cross-coupling reaction of primary trialkybismuth reagents with 2-haloazines and diazines is reported. The reaction functions with pyridines, pyrimidines, pyridazines and pyrazines and tolerates many functional groups. This method gives access to 2-alkylazines and diazines, a class of compounds which is important in medicinal chemistry.

Azines and diazines are ubiquitous in pharmaceutical industry as they can show a wide diversity of biological activities.[1] The introduction of an alkyl group alpha to the nitrogen of an azine or a diazine allows to screen the binding environment surrounding a bioactive compound[2] and to modulate its biophysical properties such as its lipophilicity, basicity, and permeability.[3] Therefore, the development of efficient and general methods that allow the preparation of 2-alkylazines and diazines is highly important for organic and medicinal chemistry. The cross-coupling of sp^3 alkylmetal species[4] with azines and diazines bearing an halogen at the 2-position is an attractive approach to access the corresponding 2-alkyl heterocyclic derivatives. However, this type of coupling is notoriously difficult and only isolated examples involving organoboronic acids,[5] organozincs,[6] organomagnesium[7] and organotin[8] reagents have been reported. In addition, some of these methods suffer from scope limitation and poor functional group tolerance, or necessitate strict anhydrous conditions or complex and costly catalysts to prevent the undesired β-hydride elimination pathway. To the best of our knowledge, there is currently no comprehensive report on the cross-coupling reaction of alkylmetals with 2-halo pyridines, pyrimidines, pyridazines and pyrazines. Consequently, there is a well justified need to develop a general procedure to accomplish this transformation.

Our group has reported over the past years a portfolio of reactions for the formation of C–C,[9] C–O,[10] and C–N[11] bonds involving organobismuth reagents. Organobismuthanes have found increasing use in bond formation due to their unique properties and reactivity.[12] These reagents, which can be easily prepared from inexpensive and non toxic bismuth salts, are very tolerant to a wide diversity of functional groups and thus represent highly attractive species for methodology development.

We recently reported the cross-coupling of trialkylbismuth reagents with aryl and heteroaryl halides and pseudo halides[13] and demonstrated that triphenethylbismuthine reacts smoothly with 2-chloro-3-cyanopyridine **1** to furnish the corresponding coupling product **2** in good yield (Scheme 1). Interestingly, and contrary to cross-coupling reactions with other alkymetal species, no product coming from the β-hydride elimination pathway could be detected under these conditions. We would like to report herein the full scope of the cross-coupling reaction of trialkylbismuthines with 2-halo- and 2-triflyl-azines and diazines **3**, a process which leads to medicinally relevant 2-alkylazines and diazines **4** (Scheme 1).

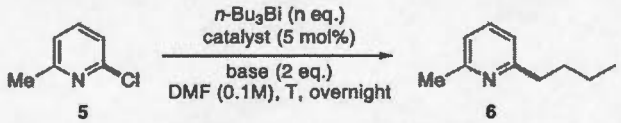


Scheme 1. Synthesis of 2-alkylazines and diazines by cross-coupling reaction involving trialkylbismuthines (FG = Functional Group)

We began by optimizing the reaction conditions for the cross-coupling reaction between tri-*n*-butylbismuthine and 2-chloro-6-methylpyridine **5** (Table 1). Tri-*n*-butylbismuthine was prepared *in situ* by the addition of *n*-butylmagnesium bromide over bismuth chloride in THF and was not isolated (see experimental section). The reaction mixture was diluted with DMF to quench any excess Grignard reagent remaining and the trialkylbismuth reagent thus formed was used directly in the cross-coupling reaction. This one-pot protocol avoids any cumbersome isolation of the air sensitive trialkylbismuthine. Using conditions that we previously reported,[13] we obtained the desired product **6** in 32% yield (entry 1). Changing the catalyst for systems that are more suited for cross-coupling reactions with aryl chorides proved inefficient in our hands (entry 2 and 3). Replacing the base by potassium phosphate proved to be

inconsequential (entry 4) and to our surprise, the reaction proceeded even in the absence of base (entry 5). While these results suggest that the choice of the base is irrelevant, we found that the yield could be substantially improved upon using cesium carbonate as the base instead of potassium carbonate (entry 6). The yield was further ameliorated by using 1.5 or 2.0 equivalents of tributylbismuth (entry 7 and 8). Performing the reaction with 1.1 or 1.5 equivalent of tributylbismuth at 130 °C in the presence of cesium carbonate provided the best yields of the coupling product (entries 9 and 10).

Table 1. Optimization of reaction conditions for the cross-coupling of tri-*n*-butylbismuthine with 2-chloro-6-methylpyridine **5**



5 6

Entry	*n*-Bu_3Bi (n equiv)	Catalyst	Base	T (°C)	Yield[a] (%)
1	1.1	$Pd(PPh_3)_4$	K_2CO_3	110	32
2	1.1	$Pd(P\text{t-}Bu_3)_2$	K_2CO_3	110	6
3	1.1	PEPPSI-IPr	K_2CO_3	110	0
4	1.1	$Pd(PPh_3)_4$	K_3PO_4	110	30
5	1.1	$Pd(PPh_3)_4$	N.A.	110	34
6	1.1	$Pd(PPh_3)_4$	Cs_2CO_3	110	54
7	1.5	$Pd(PPh_3)_4$	Cs_2CO_3	110	65
8	2.0	$Pd(PPh_3)_4$	Cs_2CO_3	110	69
9	1.1	$Pd(PPh_3)_4$	Cs_2CO_3	130	70
10	1.5	$Pd(PPh_3)_4$	Cs_2CO_3	130	66

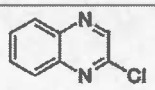
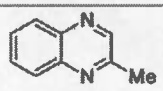
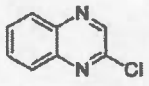
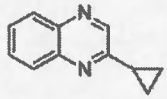
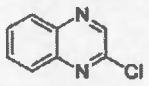
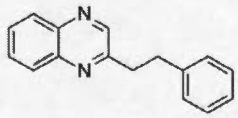
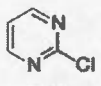
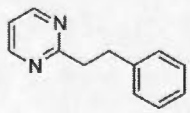
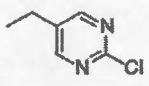
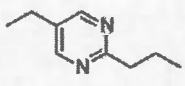
[a] Isolated yield of pure compound **6**.

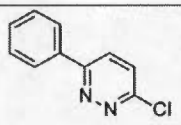
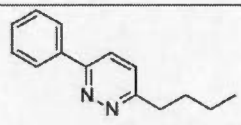
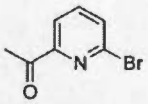
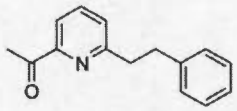
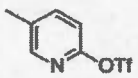
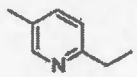
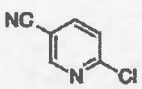
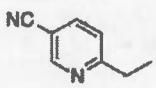
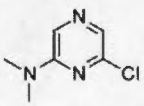
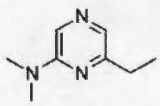
Using our optimized conditions, we next investigated the scope of the reaction by coupling different trialkylbismuthines with 2-halo- and 2-triflylazines and diazines bearing a wide range of functional groups (Table 2). In order to obtain optimal yields, we elected to perform the reaction using 1.5 equivalents of the organobismuth reagent. Firstly, the results demonstrate that the reaction functions efficiently with pyrazines (entry 1-3, 10), pyrimidines (entry 4 and 5), pyridazines (entry 6) and pyridines (entry 7-9). Secondly, the reaction furnishes the coupling product in similar yields upon using the chloro or bromo electrophile, but leads to modest yields when a 2-triflyl substrate is used (entry 8). The study indicates that functional groups such as ketones (entry 7), nitriles (entry 9), and amines (entry 10) are well tolerated. These groups can be used for further functionalization of the product, a feature which

is important for applications in medicinal chemistry. Enolizable groups that would normally not be tolerated with Grignard reagents, such as a methyl ketone (entry 7), are unaffected in the course of the reaction. Attempt at performing the reaction directly with Grignard species under iron catalysis led to the product of addition on the ketone in low yield. While the reaction functions with most primary linear alkyl groups, we found that cyclopropyl was the only secondary alkyl group capable of undergoing cross-coupling under these conditions (entry 2). Aryl and heteroaryl cyclopropanes are very useful in medicinal chemistry since the cyclopropyl group usually shows higher metabolic stability than acyclic alkyl groups in the presence of cytochromes P450.[14]

Table 2. Cross-coupling of trialkylbismuthines with 2-halo- and 2-triflylazines and diazines

3 4

Entry	Electrophile	Product	Yield[b] (%)
1	 **3a**	 **4a**	86
2	 **3a**	 **4b**	70
3	 **3a**	 **4c**	85
4	 **3d**	 **4d**	68
5	 **3e**	 **4e**	65

6	 **3f**	 **4f**	46
7	 **3g**	 **4g**	48
8	 **3h**	 **4h**	24
9	 **3i**	 **4i**	45
10	 **3j**	 **4j**	71

[a] R_3Bi (1.5 equiv), $Pd(PPh_3)_4$ (0.05 equiv), Cs_2CO_3 (2 equiv), DMF, 130 °C, overnight [b] Isolated yield of pure compounds.

In summary, we have developed a general procedure for the cross-coupling of trialkylbismuth reagents with 2-halo- and 2-triflylazines and diazines. The method operates under simple conditions using a simple catalyst. The procedure tolerates many functional groups and the compounds that are generated are highly valuable in medicinal chemistry. Studies aimed at transferring other substituted and functionalized alkyl groups are in progress in our laboratories and results will be reported in due course.

EXPERIMENTAL

All reactions were run under argon atmosphere in non flame dried glassware. Unless otherwise stated, commercial reagents were used without further purification. Grignard reagents were purchased from Aldrich or prepared using conventional methods with metallic magnesium and were titrated prior use.[15] Anhydrous bismuth chloride 99.999% was purchased from Strem Chemicals. Anhydrous solvents were obtained using a MBRAUN (model MB-SPS 800) encapsulated solvent purification system. The evolution of reactions was monitored by analytical thin-layer chromatography using silica gel 60 F254

precoated plates. Flash chromatography was performed employing 230-400 mesh silica (Silicycle) using the indicated solvent system according to standard techniques.[16] Nuclear magnetic resonance spectra (^{1}H, ^{13}C) were recorded on a Bruker Avance-III 300MHz spectrometer. Chemical shifts for ^{1}H-NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ 7.27 ppm, DMSO δ 2.54 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant *J* in Hz and integration. Chemical shifts for ^{13}C spectra are recorded in parts per million from tetramethylsilane using the central peak of deuterochloroform (77.00 ppm) as the internal standard. All ^{13}C spectra were obtained with complete proton decoupling. IR spectra were recorded on a Thermo Scientific Nicolet 6700 PT-IR from thin films and are reported in reciprocal centimeters (cm^{-1}).

General procedure for the cross-coupling reaction of trialkylbismuthines with 2-halo and 2-triflylazines and diazines

In a round-bottom flask equiped with a condenser and sparged with argon, $BiCl_3$ (144 mg, 0.46 mmol) was suspended in anhydrous THF (2.3 mL) and cooled to 0 °C. The organomagnesium reagent (1.37 mmol, THF solution) was slowly added dropwise, and the solution was stirred at 0 °C for 5 min, warmed to rt, and then heated at 65 °C for 30 min to assure complete addition of all three alkyl groups on the bismuth center. The reaction mixture was cooled to rt and diluted with anhydrous DMF (1 mL). A DMF solution of the heteroaryl halide (0.31 mmol in 3 mL) was then added, followed by Cs_2CO_3 (0.6 mmol) and $Pd(PPh_3)_4$ (18 mg, 0.015 mmol). The solution was degassed by bubbling argon during 15 min and then stirred at 130 °C for 18 h. The reaction mixture was cooled to rt, diluted with sat. aq. $NaHCO_3$ (10 mL) and extracted with EtOAc (2 x 10 mL). The combined organic phases were washed with brine (3 x 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography using the indicated solvent system to afford the desired product. When necessary, the compound was further purified by preparative thin layer chromatography using the same solvent system. The alcohol derived from the oxidation of the trialkylbismuth is sometimes observed as a side product.

2-*n*-Butyl-6-methylpyridine (6)

The general procedure was followed on a 0.39 mmol scale starting from 2-chloro-6-methylpyridine **5**. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford **6** as a colorless oil (38 mg, 66%). Spectral data was identical to literature compound.[17] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.44 (t, J = 6.2 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 2.73 (t, J = 9.1 Hz, 2H), 2.50 (s, 3H), 1.69-1.63 (m, 2H), 1.40-1.33 (m, 2H), 0.91 (t, J = 9.2 Hz, 3H).

2-Methylquinoxaline (4a)

The general procedure was followed on a 0.31 mmol scale starting from 2-chloroquinoxaline **3a**. The

crude material was purified on silica gel (40% EtOAc/hexanes) to afford **4a** as a colorless oil (38 mg, 86%). Spectral data was identical to literature compound.[18] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.07-7.98 (m, 2H), 7.75-7.65 (m, 2H), 2.76 (s, 3H).

2-Cyclopropylquinoxaline (4b)

The general procedure was followed on a 0.31 mmol scale starting from 2-chloroquinoxaline **3a**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **4b** as a colorless oil (36 mg, 70%). Spectral data was identical to literature compound.[19] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.03 (dd, J = 8.3, 1.2 Hz, 1H), 7.92 (dd, J = 8.3, 1.2 Hz, 1H), 7.70-7.58 (m, 2H), 2.29-2.21 (m, 1H), 1.26-1.23 (m, 2H), 1.18-1.13 (m, 2H).

2-Phenethylquinoxaline (4c)

The general procedure was followed on a 0.31 mmol scale starting from 2-chloroquinoxaline **3a**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **4c** as a colorless oil (60 mg, 85%). Spectral data was identical to literature compound.[20] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.13 (dd, J = 8.0, 2.0 Hz, 2H), 7.83-7.73 (m, 2H), 7.35-7.26 (m, 5H), 3.42-3.37 (m, 2H), 3.27-3.22 (m, 2H).

2-Phenethylpyrimidine (4d)

The general procedure was followed on a 0.44 mmol scale starting from 2-chloropyrimidine **3d**. The crude material was purified on silica gel (30% EtOAc/hexanes) to afford **4d** as a colorless oil (54 mg, 68%). Spectral data was identical to literature compound.[20] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.73 (d, J = 6.3 Hz, 2H), 7.35-7.22 (m, 5H), 7.13 (t, J = 8.9 Hz, 1H), 3.36-3.29 (m, 2H), 3.24-3.18 (m, 2H).

5-Ethyl-2-*n*-propylpyrimidine (4e)

The general procedure was followed on a 0.35 mmol scale starting from 2-chloro-5-ethylpyrimidine **3e**. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford **4e** as a colorless oil (28 mg, 53%): R*f* 0.30 (25% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (s, 2H), 2.88 (t, J = 8.1 Hz, 2H), 2.60 (q, J = 8.2 Hz, 2H), 1.85-1.77 (m, 2H), 1.24 (t, J = 7.9 Hz, 3H), 0.96 (t, J = 8.2 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.9, 156.4, 133.2, 41.0, 23.3, 22.1, 15.0, 13.9; IR (neat) 3431, 2960, 2926, 1713, 1633, 1466.

3-*n*-Butyl-6-phenylpyridazine (4f)

The general procedure was followed on a 0.26 mmol scale starting from 3-chloro-6-phenylpyridazine **3f**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **4f** as a colorless oil (24 mg, 46%). Spectral data was identical to literature compound.[21] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.05 (dd, J = 8.2, 1.9 Hz, 2H), 7.75 (d, J = 8.8 Hz, 1H), 7.49-7.46 (m, 3H), 7.35 (d, J = 8.8 Hz, 1H), 3.01 (t, J = 7.7 Hz, 2H), 1.82-1.74 (m, 2H), 1.46-1.39 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H).

2-Acetyl-6-phenethylpyridine (4g)

The general procedure was followed on a 0.25 mmol scale starting from 2-acetyl-6-bromopyridine **3g**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **4g** as a colorless oil (27 mg, 48%): R*f* 0.56 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 7.9, 0.7 Hz, 1H), 7.73 (t, *J* = 7.7 Hz, 1H), 7.35-7.23 (m, 6H), 3.24-3.15 (m, 4H), 2.78 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 200.8, 160.7, 153.3, 141.4, 136.9, 128.5, 128.4, 126.4, 126.1, 119.0, 39.6, 35.4, 25.8; IR (neat) 3027, 2920, 1697, 1586, 1453, 1355.

2-Ethyl-5-methylpyridine (4h)

The general procedure was followed on a 0.21 mmol scale starting from 2-triflyl-5-methylpyridine **3h**. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford **4h** as a colorless oil (6 mg, 24%). Spectral data was identical to literature compound.[22] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.34 (d, *J* = 1.5 Hz, 1H), 7.41 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.06 (d, *J* = 7.9 Hz, 1H), 2.79 (q, *J* = 7.3 Hz, 2H), 2.29 (s, 3H), 1.28 (t, *J* = 7.6 Hz, 3H).

6-Ethyl-3-cyanopyridine (4i)

The general procedure was followed on a 0.36 mmol scale starting from 6-chloro-3-pyridinecarbonitrile **3i**. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford **4i** as a colorless oil (17 mg, 40%). Spectral data was identical to literature compound. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.73 (d, *J* = 1.6 Hz, 1H), 7.80 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 1H), 2.83 (q, *J* = 7.6 Hz, 2H), 1.26 (t, *J* = 7.6 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) 168.1, 152.1, 139.4, 122.2, 117.0, 107.2, 31.8, 13.3; IR (neat) 3432, 2972, 2933, 2232, 1594, 1484.

2-Ethyl-6-dimethylaminepyrazine (4j)

The general procedure was followed on a 0.32 mmol scale starting from 2-chloro-6-dimethylamine pyridine **3j**. The crude material was purified on silica gel (35% EtOAc/hexanes) to afford **4j** as a colorless oil (34 mg, 71%): R*f* 0.36 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.65 (s, 1H), 3.08 (s, 6H), 2.62 (q, *J* = 7.6 Hz, 2H), 1.25 (t, *J* = 7.6 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 155.6, 154.5, 130.0, 126.7, 37.4, 28.5, 13.3; IR (neat) 2967, 2933, 1575, 1529, 1423, 1194.

ACKNOWLEDGEMENTS

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ANNEXE B

"PALLADIUM-CATALALYZED CROSS-COUPLING REACTION OF TRIALKYLBISMUTHINES WITH 2-HALOZINES AND DIAZINES"
SUPPORTING INFORMATION

Heterocycles, **2014**, Vol. 88, No.2

DOI : 10.3987/COM-13-S(S)114

Titre : Palladium-Catalyzed Cross-Coupling Reaction of Trialkylbismuthines with 2-Haloazines and Diazines

Auteurs : Pauline Petiot et Alexandre Gagnon*


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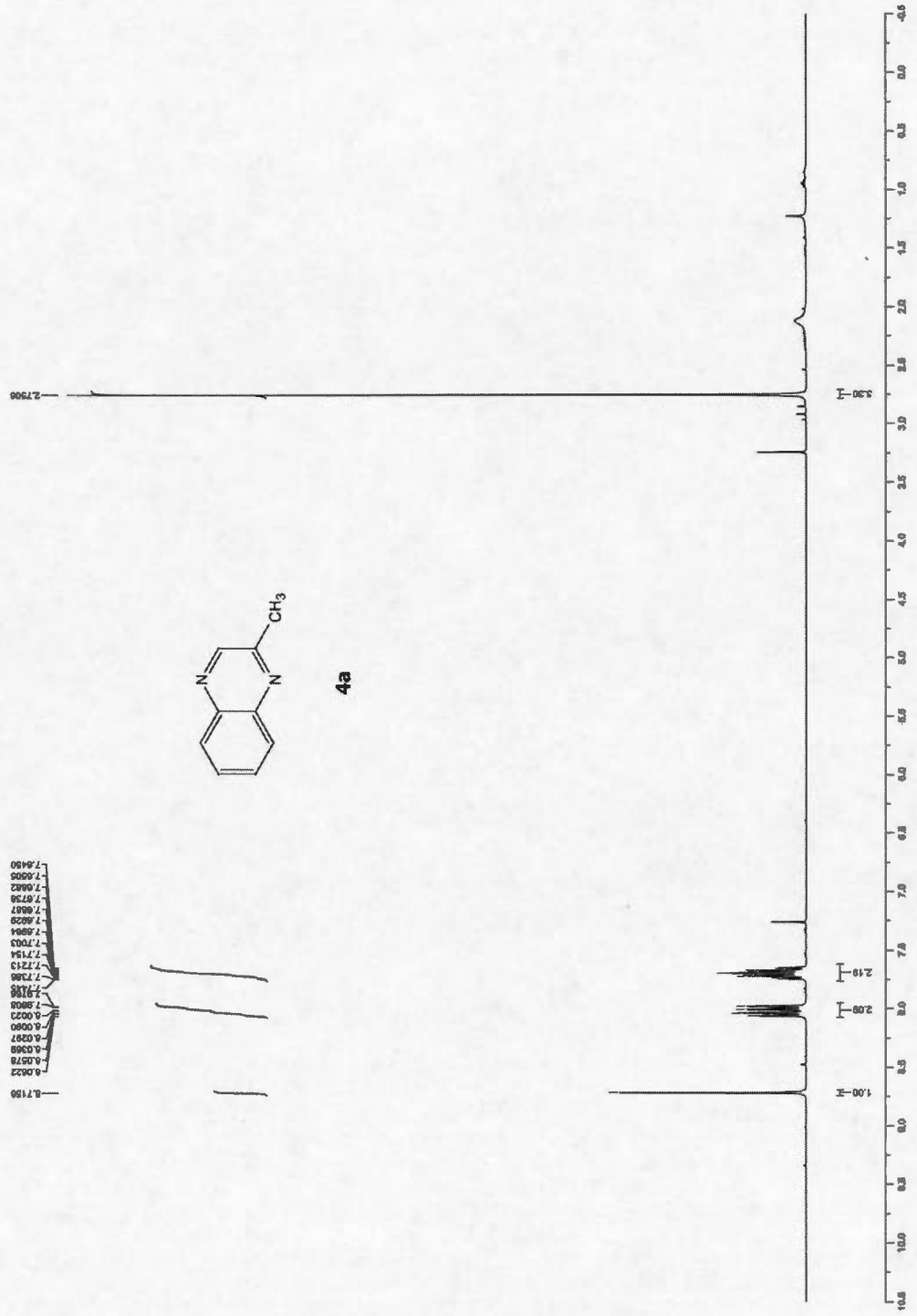
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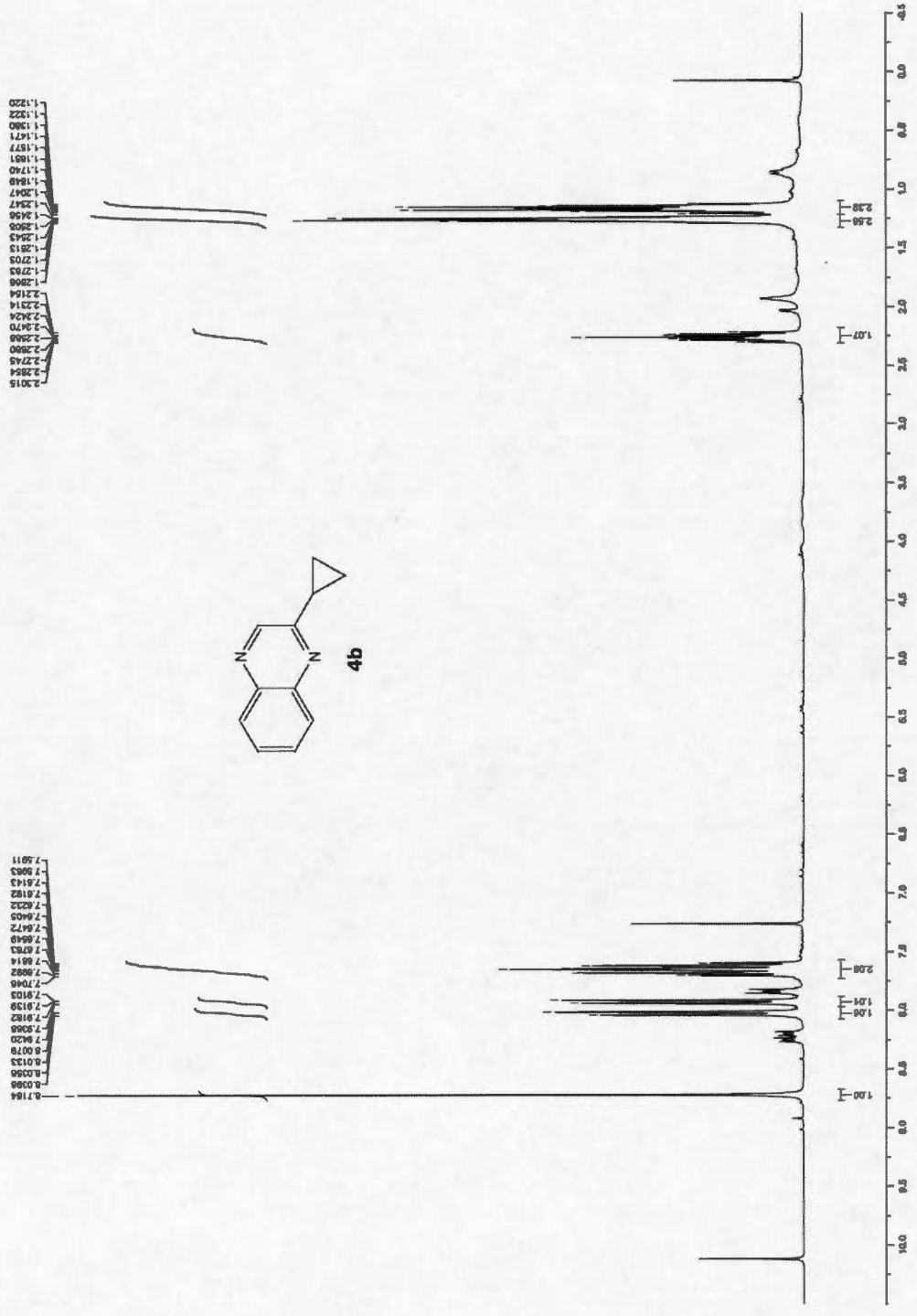
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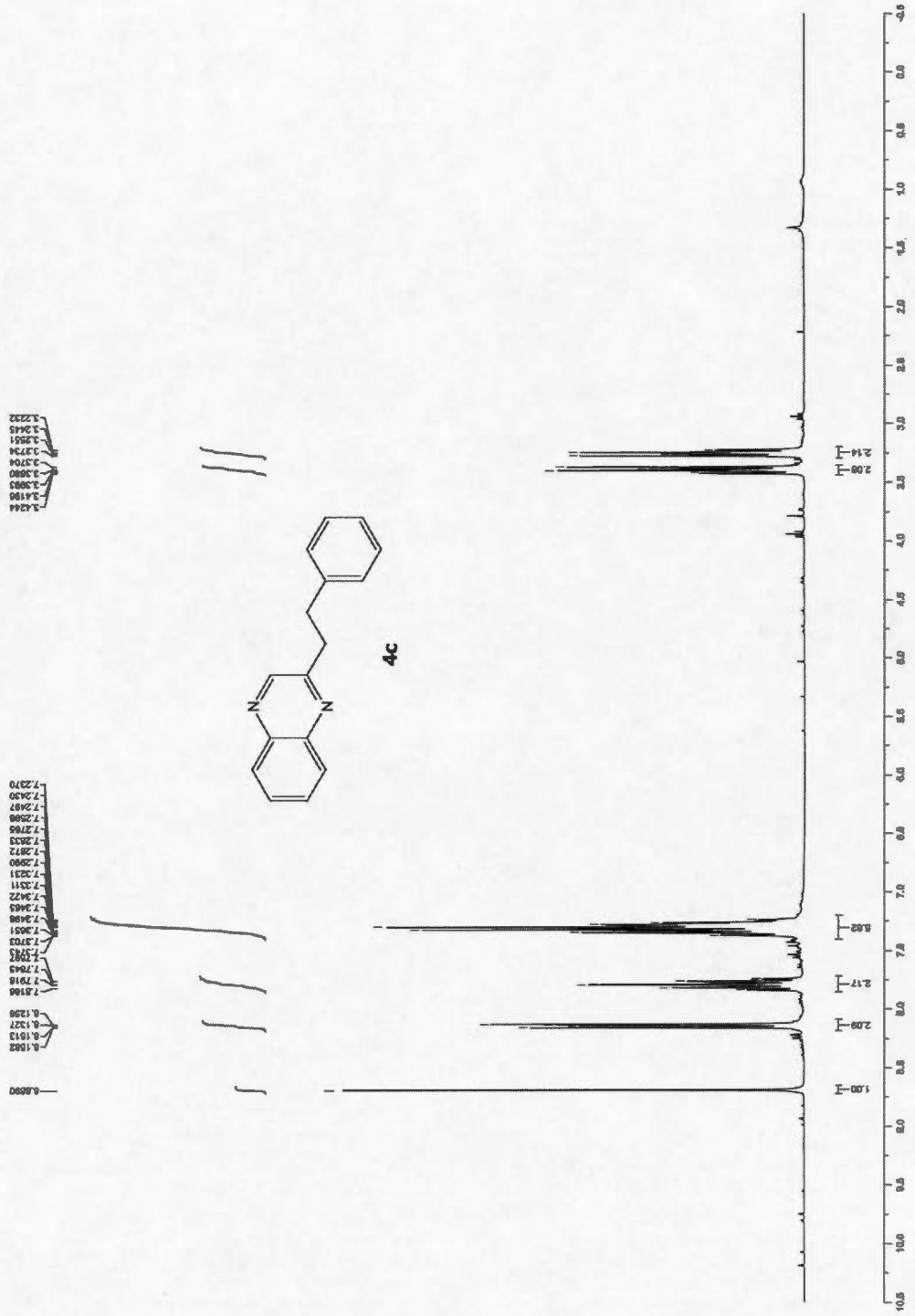
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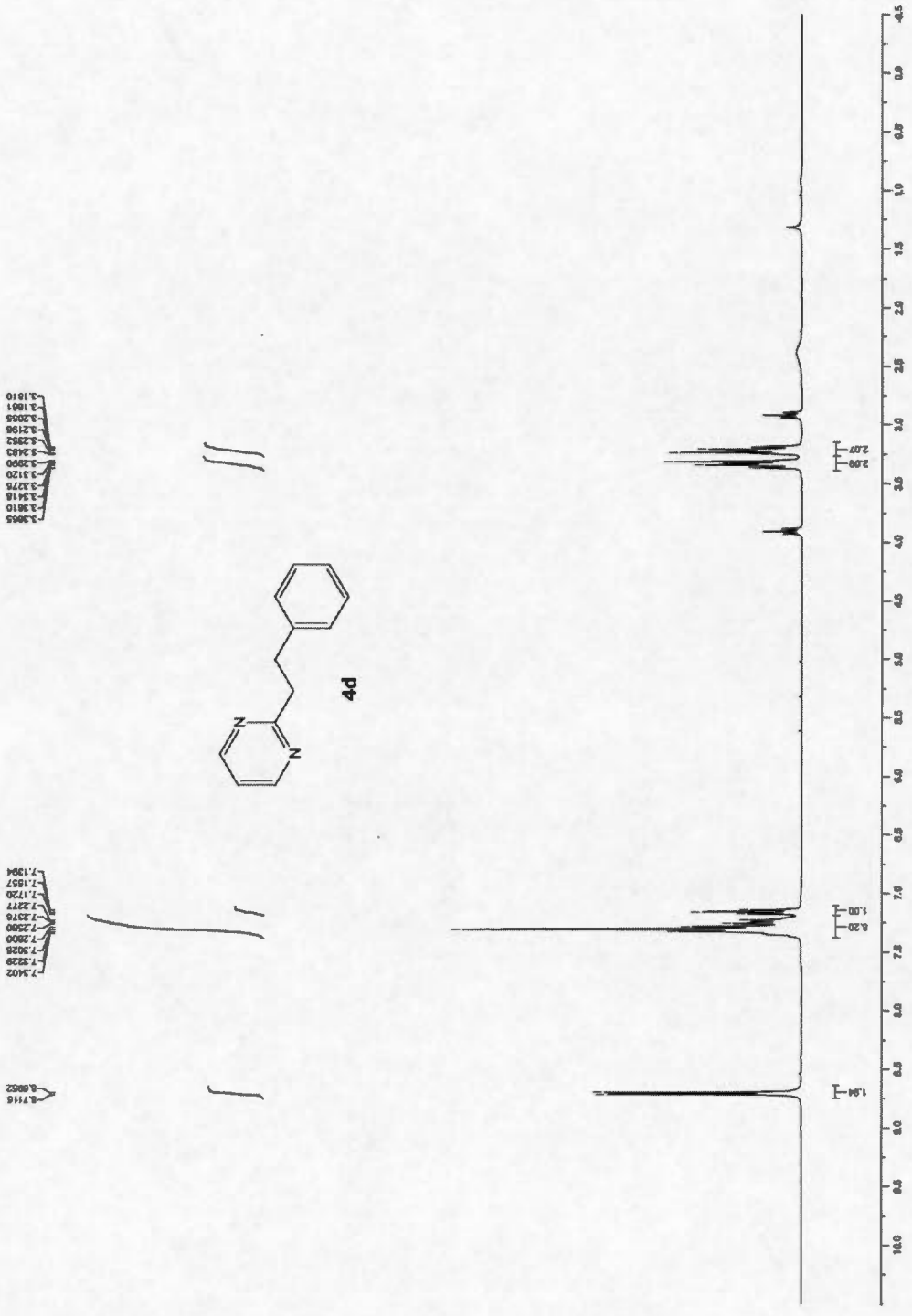
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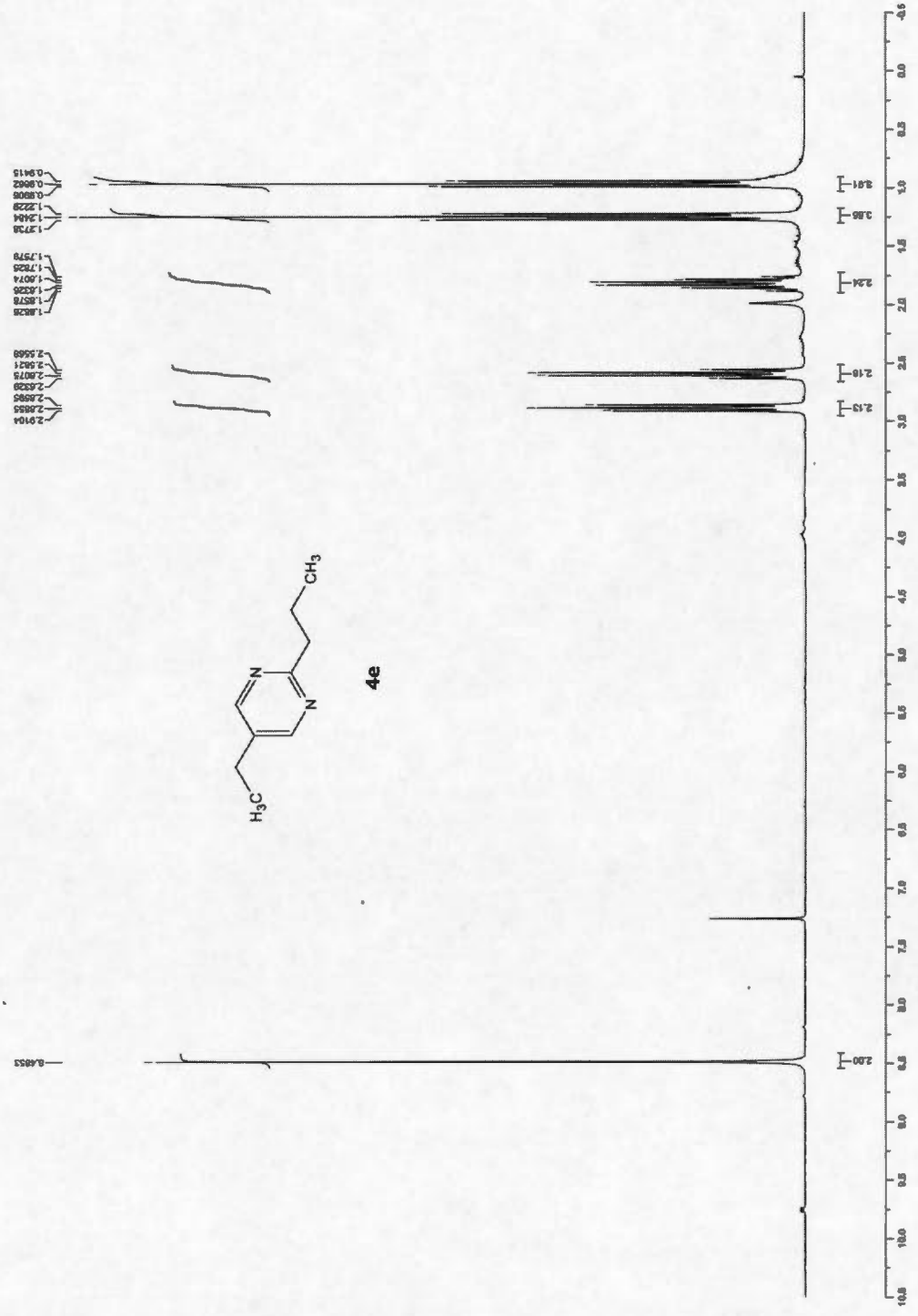
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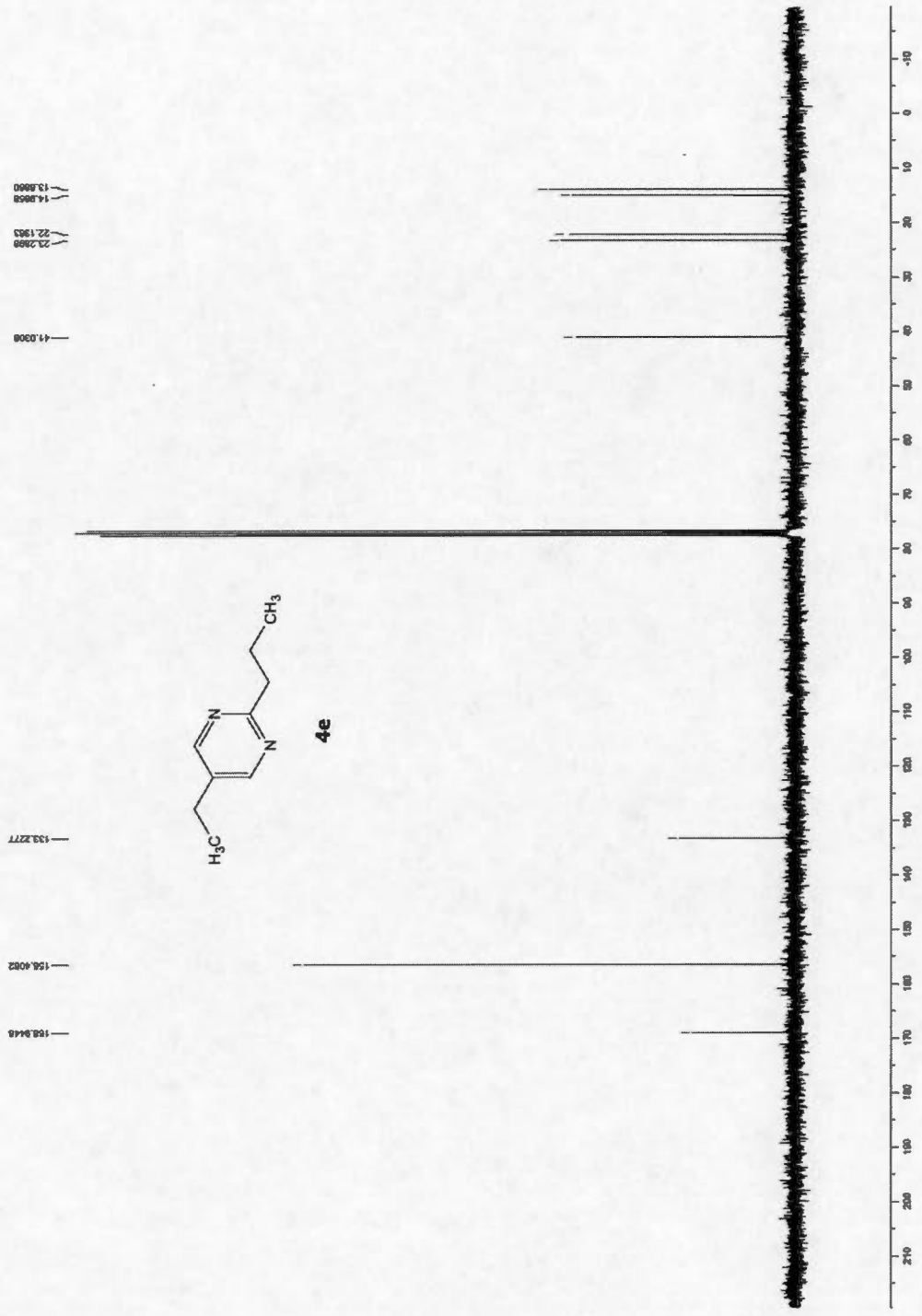
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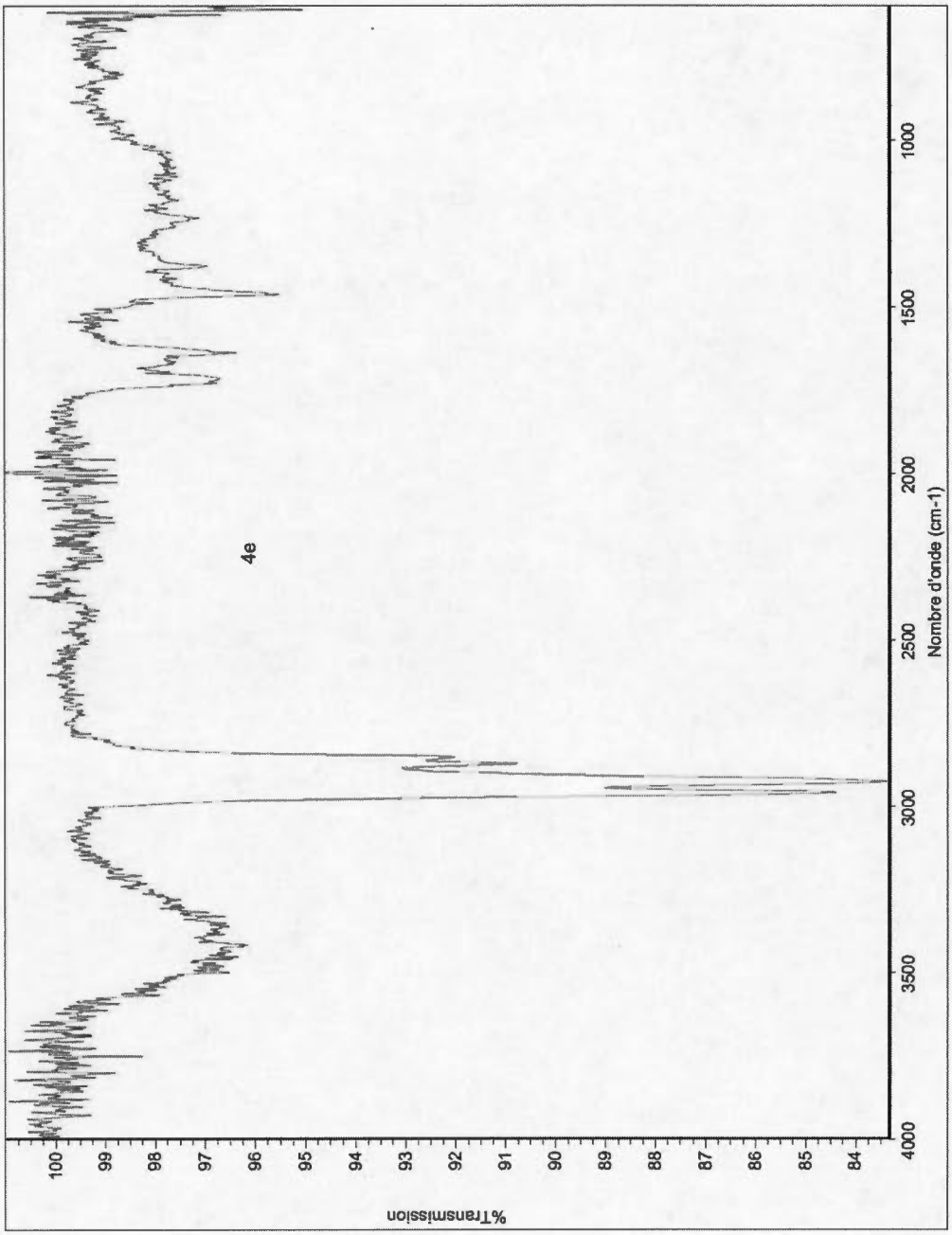
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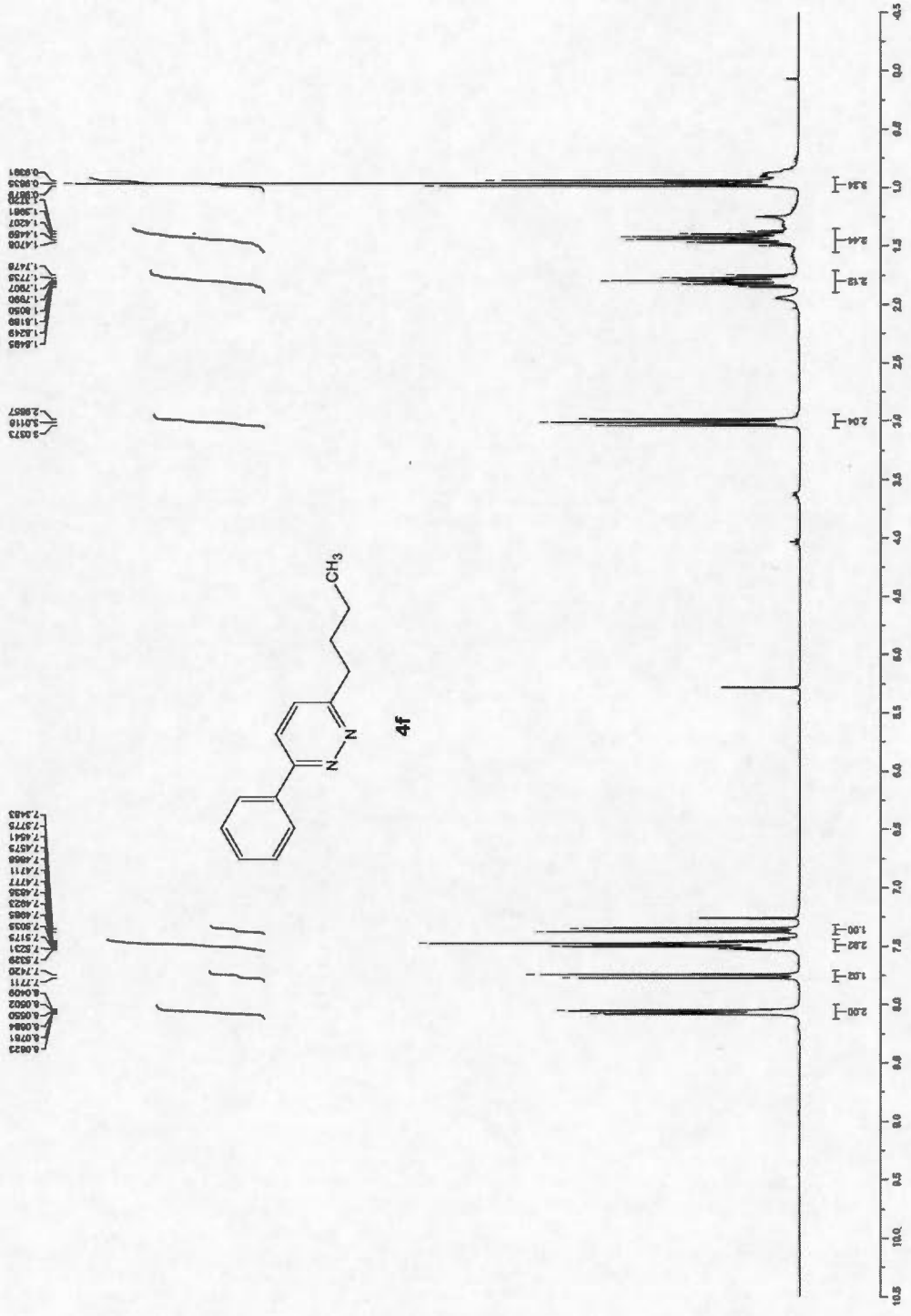
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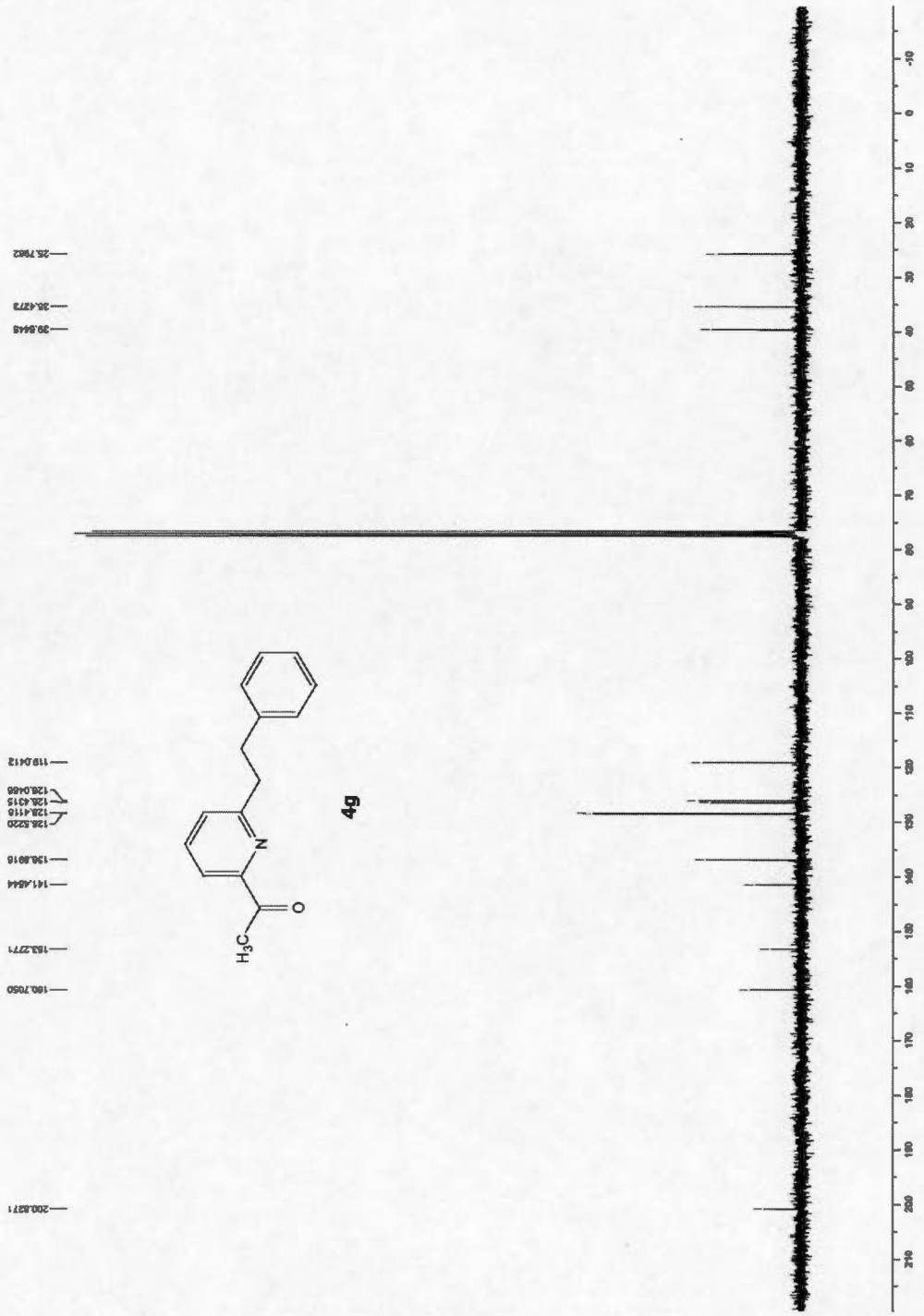
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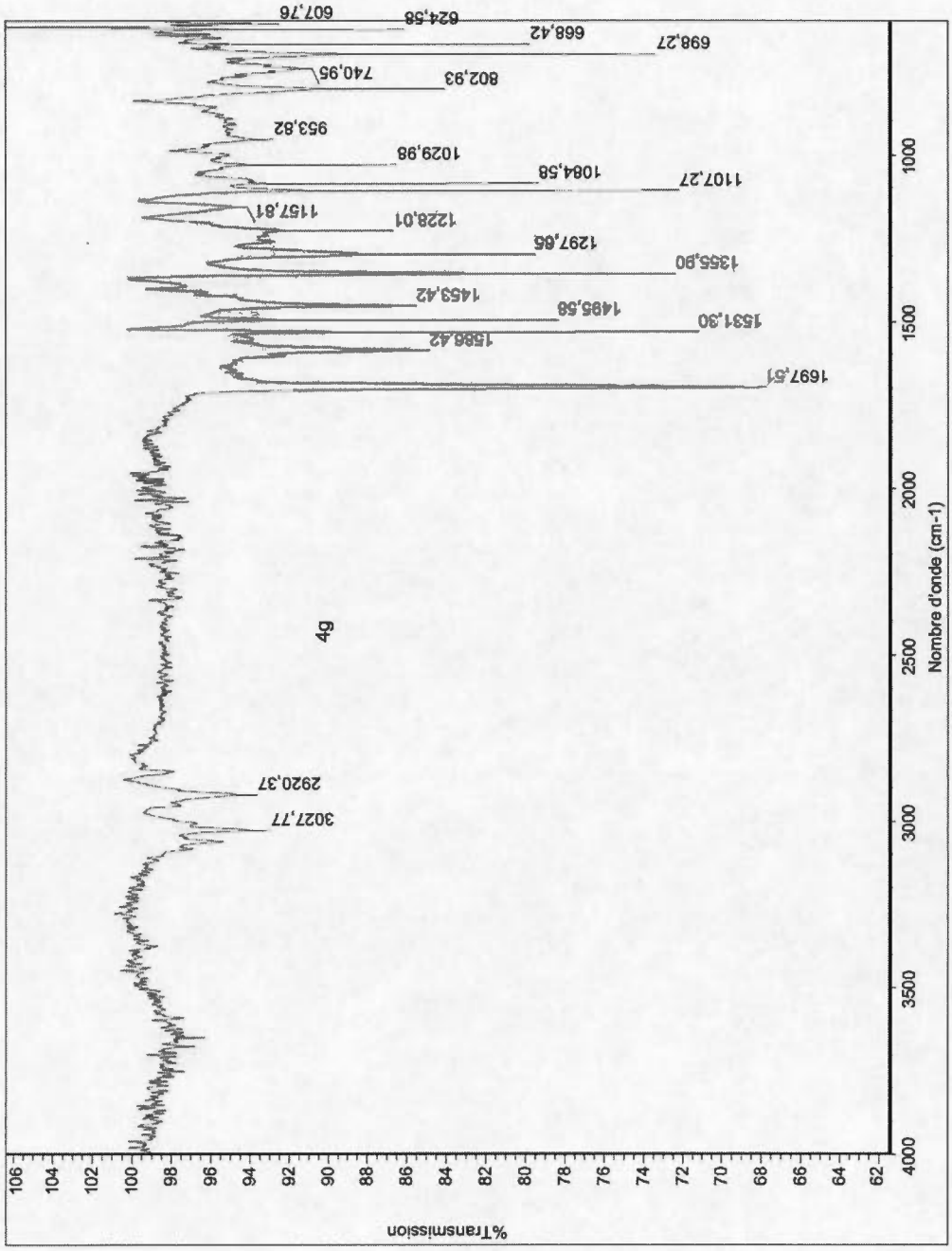
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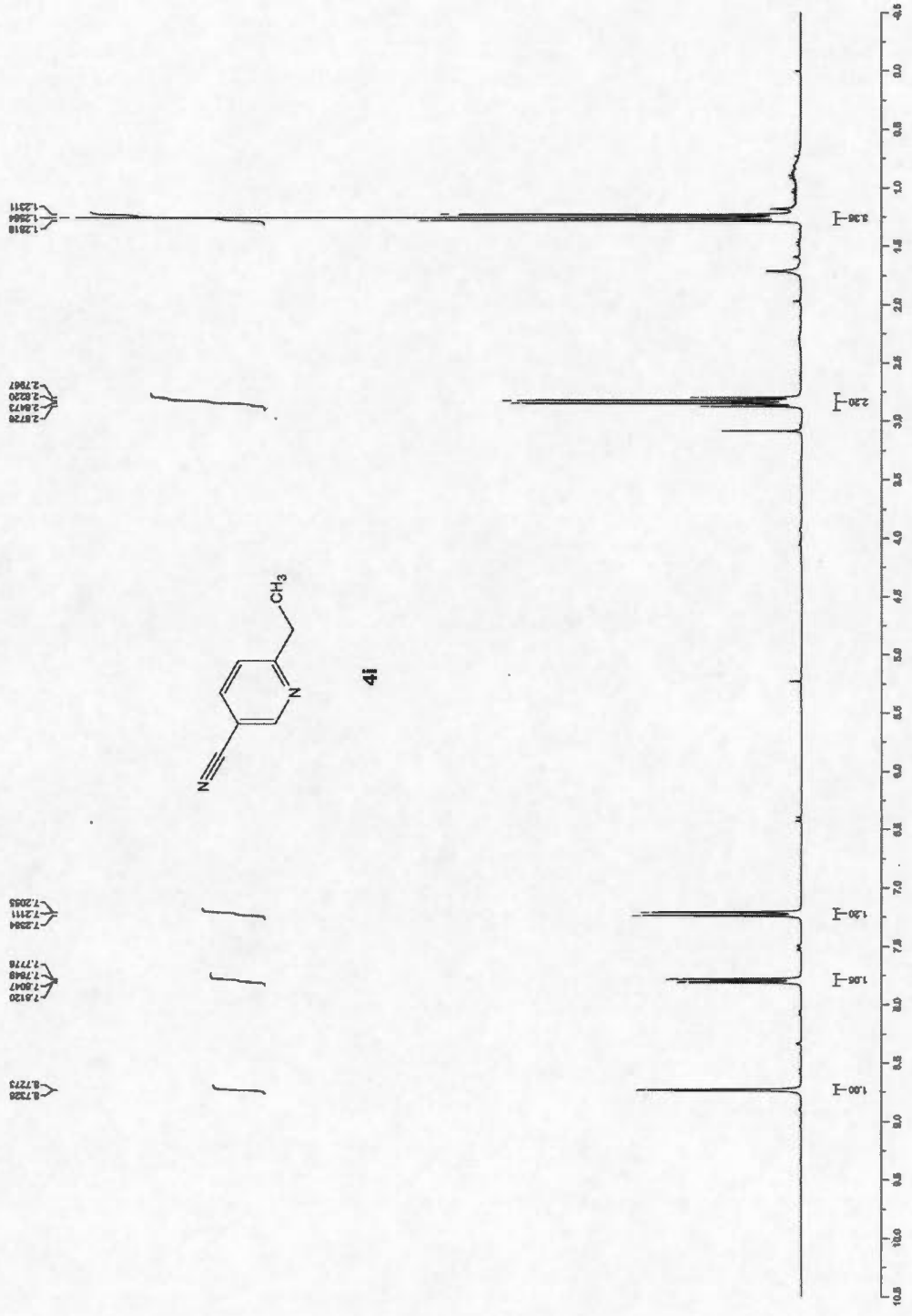
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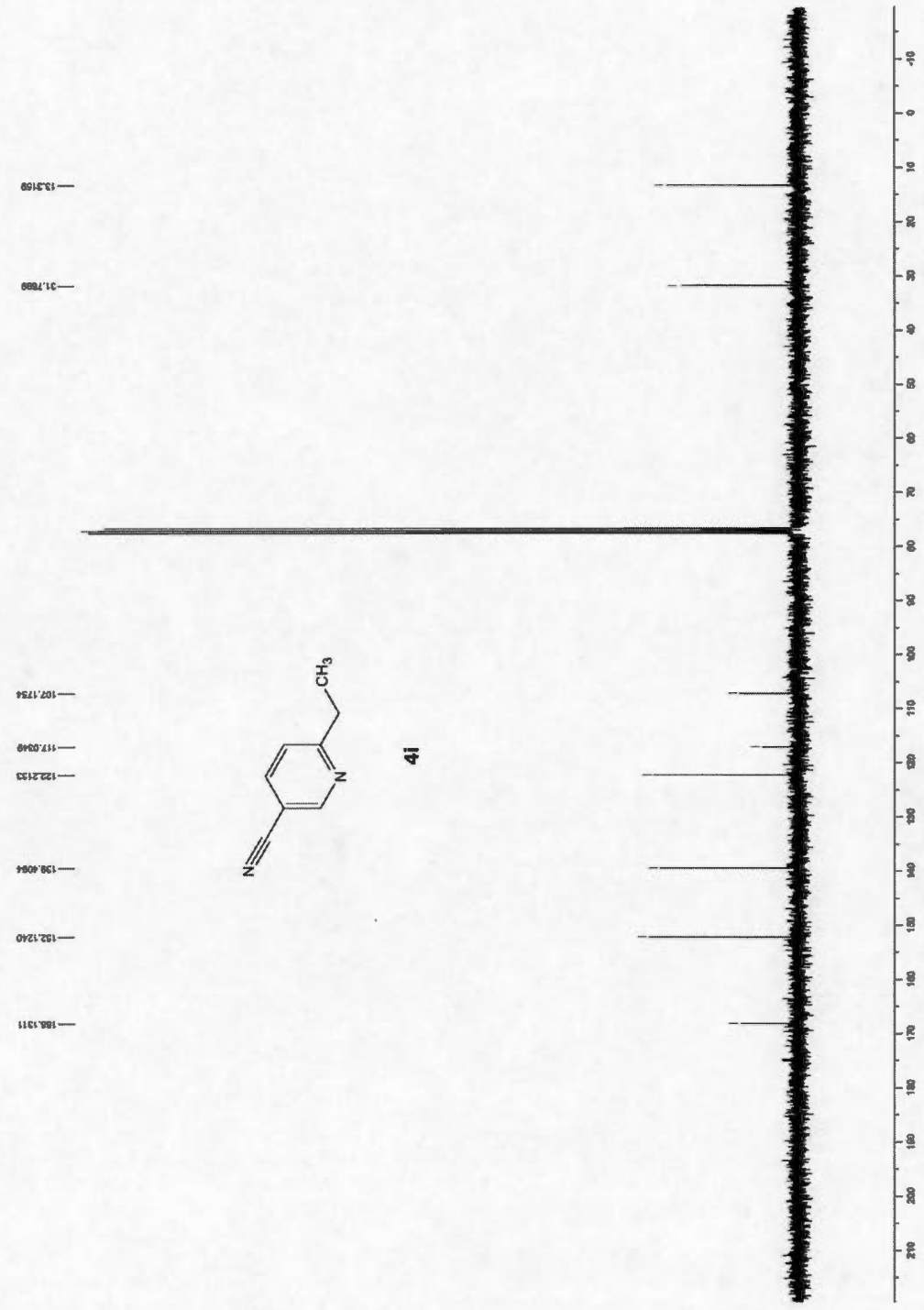
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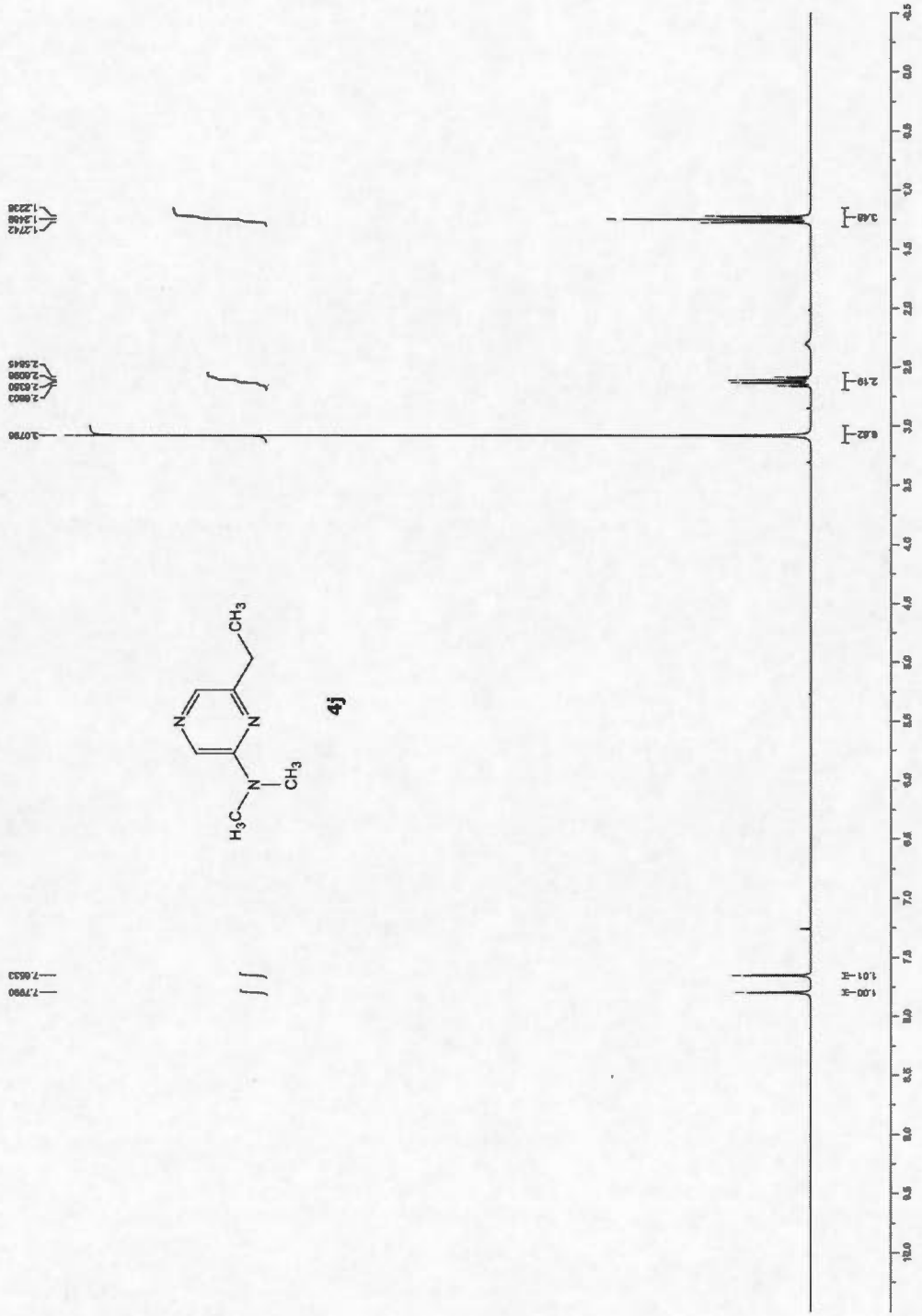
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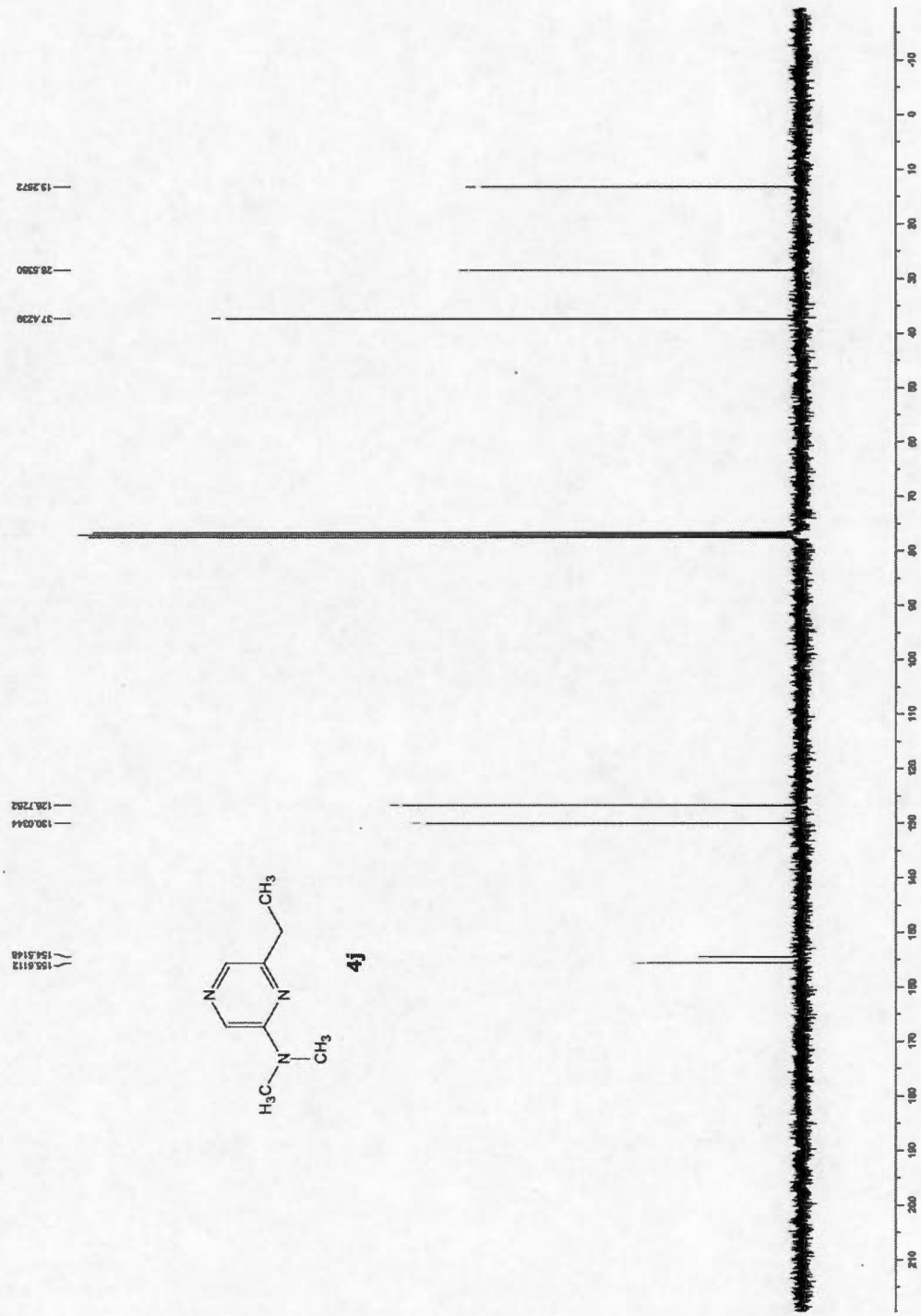
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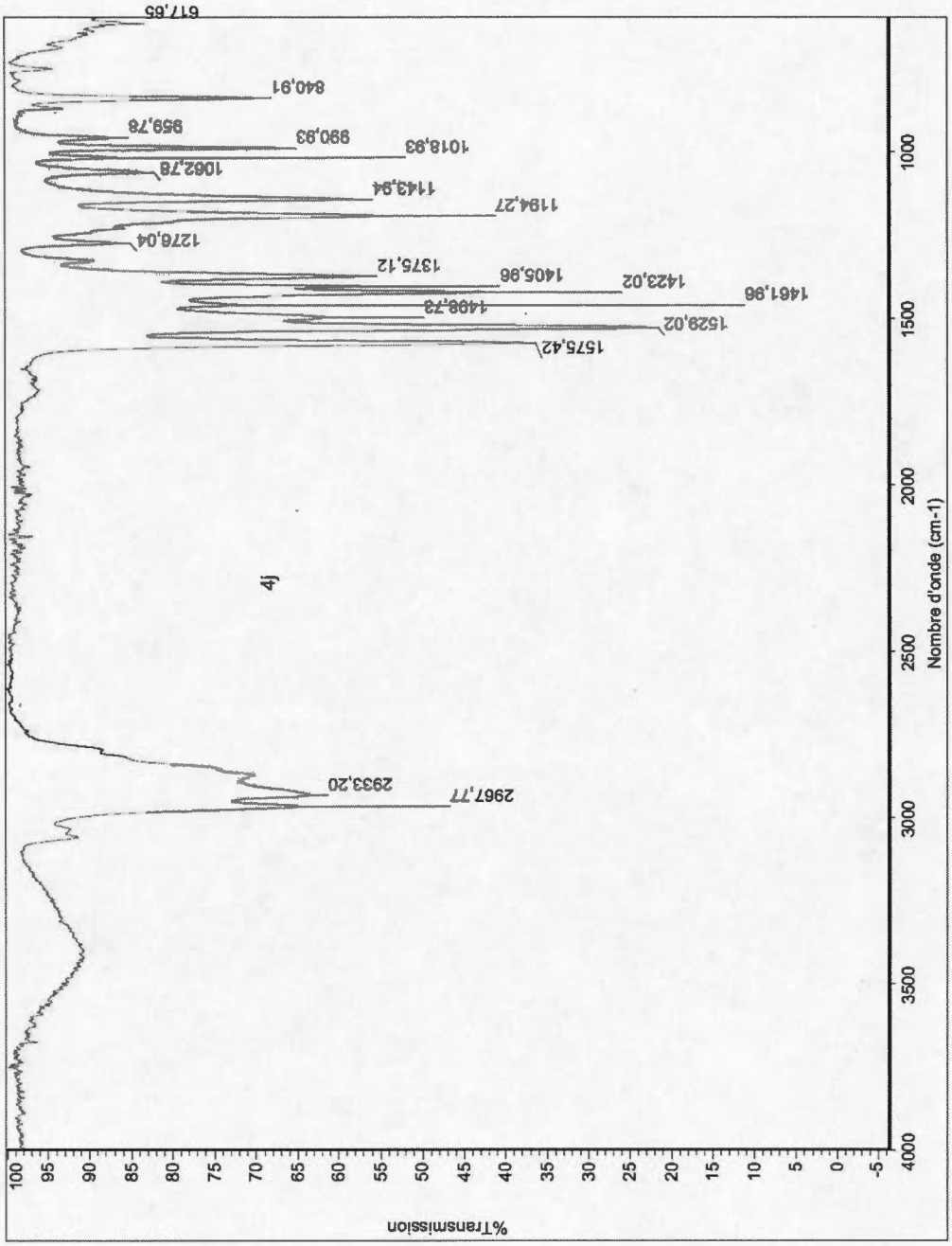
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ANNEXE C

"PALLADIUM-CATALYZED CROSS-COUPLING REACTION OF FUNCTIONALIZED ARYL- AND HETEROARYLBISMUTHANES WITH 2-HALO(OR 2-TRIFLYL)AZINES AND DIAZINES" ARTICLE

Eur. J. Org. Chem. **2013**, 5282

DOI : 10.1002/ejoc.201300850

Titre : Palladium-Catalyzed Cross-Coupling Reaction of Functionnalized Aryl- and Heteroarylbismuthanes with 2-Halo(or 2-Triflyl)azines and -diazines

Auteurs : Pauline Petiot et Alexandre Gagnon*

SHORT COMMUNICATION

EurJOC

DOI: 10.1002/ejoc.201300850

Palladium-Catalyzed Cross-Coupling Reaction of Functionalized Aryl- and Heteroarylbismuthanes with 2-Halo(or 2-Triflyl)azines and -diazines

Pauline Petiot[a] and Alexandre Gagnon*[a]

Keywords: Bismuth / Cross-coupling / Nitrogen heterocycles / Palladium / Azines

The palladium-catalyzed cross-coupling of highly functionalized organobismuthanes with 2-halo(or 2-triflyl)pyridines, -pyrimidines, -pyrazines, and -pyridazines is reported. The reaction tolerates numerous functional groups, including aldehydes. The synthesis of a shelf-stable (formylphenyl)bismuth reagent and its use in a cross-coupling reaction is also described.

Introduction

Azines and diazines are ubiquitous in pharmaceutical industry. Compounds that incorporate these heterocycles have been found to possess antimicrobial, antiviral, antioxidant, antitumoral, anti-inflammatory, and other activities.[1] Azines and diazines have also been used in the preparation of materials that show interesting electrical and optical properties.[2] Consequently, access to efficient and general methods that allow their preparation is of utmost importance.[3] To be applicable to the context of drug discovery, these methods should tolerate the presence of functional groups that can serve as handles for further transformation of the molecule.[4] Ideally, the protocol should also involve reagents that can be easily manipulated and should operate under simple conditions that can be amenable to parallel chemistry.[5]

The metal-catalyzed cross-coupling reaction between halogenated electrophiles and organometallic reagents has evolved into an extremely powerful approach for the installation of aromatic and heteroaromatic units onto a variety of scaffolds.[6] The cross-coupling of aryl- and heteroarylmetal compounds with 2-halo(or 2-triflyl)azines and -diazines constitutes an attractive approach to access the corresponding 2-arylheterocycles. A few examples of cross-coupling reactions between organometallic reagents and 2-haloazines and -diazines have been reported.[7,8] However, many of these methods show modest substrate scope and require air- and moisture-sensitive reagents or complex catalysts. More importantly, limited functional group tolerance is often observed, particularly in the case of reactive organometallic species such as organomagnesium reagents.[9] Although organostannanes are more tolerant to acidic and electrophilic groups,[10] their high toxicity combined with the fact that only one aryl group is usually transferred make them considerably less attractive. Coupling of 2-haloazines and -diazines with organozinc reagents offers a great solution to issues of functional group tolerance.[11] However, these species must imperatively be manipulated under inert and anhydrous conditions, which complicates their use in parallel chemistry. To the best of our knowledge, the most general methods for the transfer of aryl and heteroaryl units onto azines and diazines are those of Knochel[12,13] and Quéguiner.[14] However, as these procedures involve organomagnesium reagents, sensitive groups such as aldehydes and ketones cannot be present on either coupling partner.

Organobismuthanes have found increasing use in bond formation owing to their unique properties and reactivity.[15] These organometallic reagents can be easily prepared,[16] chromatographed, and stored in air at room temperature. In addition, their low toxicity makes them extremely attractive species for methodology development. The low polarity of the C–Bi bond provides a moderate reactivity for this class of reagents, which thus allows the presence of numerous reactive or acidic functional groups on the electrophilic partner. Cross-coupling reactions involving triphenylbismuth was first reported by Barton et al. in 1988.[17] Recently, the groups of Rao,[18] Tanaka,[19] and others[20] have extended the scope of this reaction to include other organobismuthanes. However, to the best of our knowledge, the full potential of organobismuthanes in the transfer of highly functionalized groups onto 2-halo(or 2-triflyl)azines and -diazines has never been demonstrated.

We reported over the past years applications of trivalent[21,22] and pentavalent organobismuthanes[23] for the formation of C–C and C–N bonds. Recently, we disclosed the first palladium-mediated cross-coupling reaction of tri-

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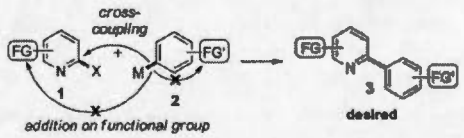
alkylbismuth reagents with a variety of scaffolds possessing reactive functional groups, including one example involving a 2-chloropyridine.[24] We report herein our study on the cross-coupling reaction of 2-halo(or 2-triflyl)pyridines, -pyrazines, -pyrimidines, and -pyridazines with functionalized aryl- and heteroarylbismuthanes.

To have high value, we aimed for a protocol that would involve a simple catalyst, shelf-stable organometallic species and that would permit the cross-coupling between two units that both possess sensitive functional groups. Functionalized organometallics are extremely valuable species in organic synthesis.[25] However, one of the major issue consists in designing an organometallic reagent that will selectively react at the desired position of the heterocycle without attacking the functional groups present on the electrophile or on the organometallic species (Scheme 1). We report herein our results on the preparation of organobismuthanes that bear functionalized groups, that are shelf-stable and that can be used in palladium-catalyzed C–C bond-forming reactions.



Scheme 1. Chemoselectivity of a cross-coupling reaction between functionalized organometallic species and 2-halopyridines. FG, FG' = functional group; M = metal; X = halide or pseudohalide.

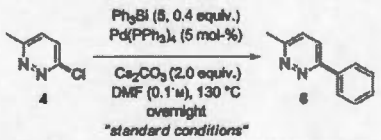
Results and Discussion

Before exploring functional group compatibility, we began by optimizing the reaction conditions for the coupling of triphenylbismuth (0.4 equiv.) with chlorodiazine **4**. Using conditions that we previously reported for the coupling of tricyclopropylbismuth[21] and other trialkylbismuthanes,[24] we obtained 65% yield of desired product **6** (Table 1, Entry 1).

To assure that all three aryl groups were effectively transferred, we verified that the yield of product **6** was the same upon using 0.7 and 1.1 equiv. of triphenylbismuth (Table 1, Entries 2 and 3). The fact that similar yields were obtained demonstrate that all three phenyl groups were indeed transferred during the process. This well-established characteristic of triarylbismuth reagents makes them more atom-economical than other reagents such as aryltrialkyltin species. Performing the reaction at higher temperatures under thermal (Table 1, Entry 4) or microwave conditions (Table 1, Entry 5) did not lead to any improvement in the yield of the reaction. Doubling the catalyst loading (Table 1, Entry 6) or changing the system to favor oxidative addition in C–Cl bonds (Table 1, Entry 7; Cy = cyclohexyl) gave a performance similar to that of the standard conditions. Surprisingly, attempts at using Buchwald phosphanes did not provide any improvement in the yield of the reaction.[26] Although changing the solvent to *N*-methylpyrrolidone (NMP) or toluene gave a lower yield of the coupling product (Table 1, Entries 8 and 9), we found that the use of a 4:1 mixture of DMF/hexamethylphosphoramide (HMPA) gave a noticeable improvement in the efficiency of the reaction (Table 1, Entry 10). To evaluate the importance of the base, we then conducted a reaction without cesium carbonate and obtained the desired product in 42% yield (Table 1, Entry 11); this suggests that – although the base is not essential – it is still required to achieve optimal yields. The results of the optimization of the reaction conditions demonstrate that the cross-coupling transformation can be accomplished by using very simple conditions and requires only approximately one third of an equivalent of the triarylbismuth reagent.

We next studied the substrate scope by using pyrazines **7**, pyrimidines **8**, pyridines **9**, and pyridazines **10** (Table 2).

Table 1. Optimization of the reaction conditions.

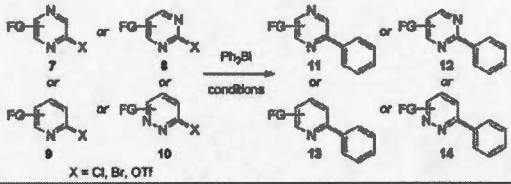


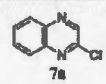
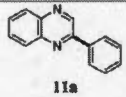
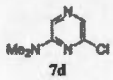
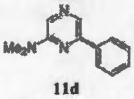
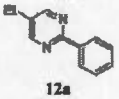
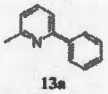
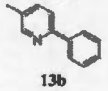
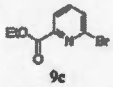
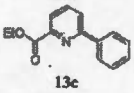
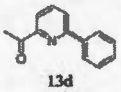
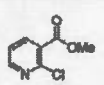
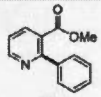
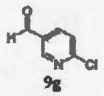
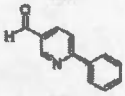
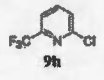
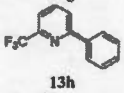
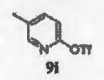
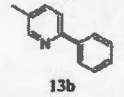
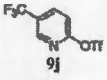
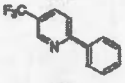
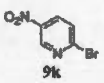
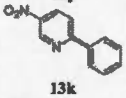
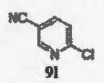
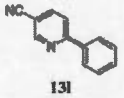
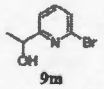
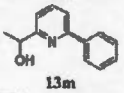
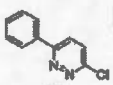
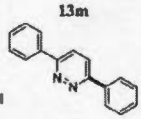
Entry	Change from "standard conditions"	Isolated yield [%][a]
1	no change	65
2	0.7 equiv. Ph_3Bi instead of 0.4 equiv.	62
3	1.1 equiv. Ph_3Bi instead of 0.4 equiv.	60
4	150 °C instead of 130 °C	50
5	170 °C (microwave) instead of 130 °C	36
6	10 mol-% $Pd(PPh_3)_4$ instead of 5 mol-%	60
7	$Pd(OAc)_2$ (5 mol-%)/PCy_3 (10 mol-%) instead of $Pd(PPh_3)_4$	50
8	NMP instead of DMF	10
9	toluene instead of DMF	50
10	DMF/HMPA (4:1) instead of DMF	72
11	no base	42

[a] Yield of isolated pure product **6**.

To compare the relative reactivity of these four classes of electrophiles, we performed all cross-coupling reactions by using triphenylbismuth under the optimal conditions found in Table 1 (Entry 1, 2, or 10). We found that pyrazines smoothly underwent the cross-coupling reaction with Ph_3Bi to provide the desired products in good to excellent yields

Table 2. Coupling of triphenylbismuth with halo(or triflyl)azines and -diazines.



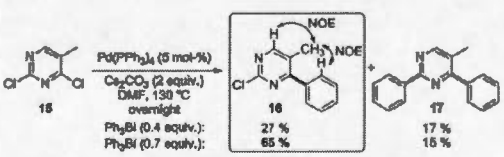
Entry	Conditions[a]	Electrophile	Product	Yield [%][b]
1	A	 7a	 11a	90
2	A	 7b	 11b	81
3	A	 7c	 11c	62
4	B	 7d	 11d	72
5	A[d]	 8a	 12a	62
6	A	 9a	 13a	65
7	B	 9b	 13b	90
8	A	 9c	 13c	50
9	C	 9d	 13d	76
10	A	 9e	 13e	50
11	A	 9f	 13e	42
12	B	 9g	 13g	80
13	B	 9h	 13h	85
14	B	 9i	 13b	66
15	B	 9j	 13j	80
16	A	 9k	 13k	45
17	A	 9l	 13l	62
18	A	 9m	 13m	30
19	A	 10a	 14a	90

[a] Conditions A: Ph_3Bi (0.4 equiv.), $Pd(PPh_3)_4$ (5 mol-%), Cs_2CO_3 (2 equiv.), DMF, 130 °C, overnight. Conditions B: Ph_3Bi (0.7 equiv.), $Pd(PPh_3)_4$ (5 mol-%), Cs_2CO_3 (2 equiv.), DMF, 130 °C, overnight. Conditions C: Ph_3Bi (0.4 equiv.), $Pd(PPh_3)_4$ (5 mol-%), Cs_2CO_3 (2 equiv.), DMF/HMPA (4:1), 130 °C, overnight. [b] Yield of isolated pure product. [c] 10 mol-% of $Pd(PPh_3)_4$ instead of 5 mol-%.

(Table 2, Entries 1–4). Electron-withdrawing and electron-donating groups had little impact on the outcome of the reaction (Table 2, Entry 3 vs. 4). We next turned our attention to pyrimidines and obtained a good yield of the desired product upon coupling triphenylbismuth with 2-chloro-5-ethylpyrimidine (**8a**; Table 2, Entry 5). We demonstrated previously that 2-chloropyridines are very competent electrophiles in cross-coupling reactions with trialkylbismuth reagents.[24] We wanted to extend the scope of the reaction to include bromo and triflyl derivatives. Our results show that 2-bromopyridines are generally more reactive than the 2-chloro analogues (e.g., **9b** vs. **9a**, **9e** vs. **9f**), which is consistent with a palladium-mediated pathway that involves oxidative addition in the C–X bond. In fact, 2-fluoropyridines failed to react under our conditions. Gratifyingly, 2-triflyl derivatives were found to have similar reactivity to the chloro analogues (e.g., **9i** vs. **9a**). These substrates can be easily accessed from the corresponding 2-hydroxypyridines. Finally, we performed the coupling reaction on 2-chloropyridazine (**10a**) and obtained desired product **14a** in excellent yield (Table 2, Entry 19).

These results show that a great diversity of functional groups are tolerated in this reaction, including amines (Table 2, Entry 4), esters (Table 2, Entries 8, 10, and 11), aldehydes (Table 2, Entry 12), nitro groups (Table 2, Entry 16), nitriles (Table 2, Entries 3 and 17), and trifluoromethyl groups (Table 2, Entries 13 and 15). Even acidic and enolizable groups such as methyl ketones (Table 2, Entry 9) and alcohols (Table 2, Entry 18) are tolerated in this reaction. This is in sharp contrast to coupling reactions involving organomagnesium reagents in which these types of groups are generally incompatible with the very reactive nature of these organometallic species.

We next studied the regioselectivity of the cross-coupling reaction involving 2,4-dichloro-5-methylpyrimidine (**15**, Scheme 2). Upon using 0.4 equiv. of triphenylbismuth, a mixture of mono- and diphenyl products **16** and **17** was obtained in modest yield, and there was a slight preference for the compound resulting from the coupling at the 4-position (as indicated by NOE experiments). Fortunately, the yield of monophenyl compound **16** could be considerably ameliorated, without increasing the amount of diphenyl product **17**, by using 0.7 equiv. of triphenylbismuth.



Scheme 2. Regioselectivity of cross-coupling between triphenylbismuth and 2,4-dichloro-5-methylpyrimidine (**15**).

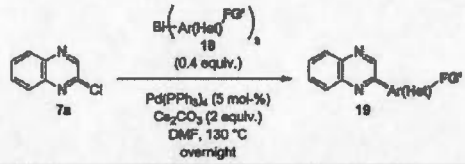
To explore the full potential of organobismuthanes in the transfer of highly functionalized groups, we next prepared functionalized organobismuth reagents **18a–j** and coupled them with 2-chloroquinoxaline (**7a**, Table 3). In general, similar yields were obtained for triarylbismuthanes possessing electron-neutral (Table 3, Entries 1 and 7), electron-withdrawing (Table 3, Entries 3, 5, and 6), and electron-donating groups (Table 3, Entries 4 and 8). Under our standard conditions, *para*- (Table 3, Entries 1, 3, 6, and 8) and *meta*- (Table 3, Entries 4, 5, and 7) -substituted aryl groups were efficiently transferred by using the corresponding organobismuthanes. To our surprise, the coupling of *ortho*-substituted aryl groups proved to be more difficult than anticipated, as only a modest yield of the desired product was obtained (Table 3, Entry 2). Acid-sensitive groups such as acetals were well tolerated in this protocol (Table 3, Entries 7 and 8). Reactive electrophilic groups such as nitriles (Table 3, Entry 5) and esters (Table 3, Entry 6) were unaffected during the transformation, which demonstrates the mildness of the cross-coupling reaction with organobismuthanes. Finally, a 2-thienyl (Table 3, Entry 9) and a 3-quinolinyl (Table 3, Entry 10) unit were installed uneventfully on the quinoxaline by using our procedure.

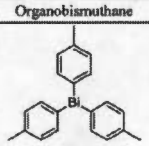
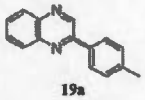
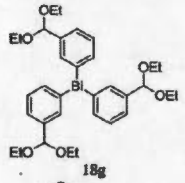
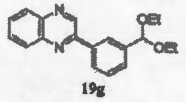
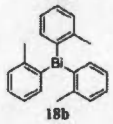
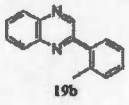
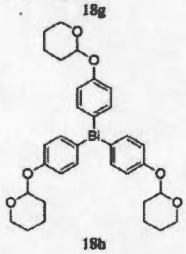
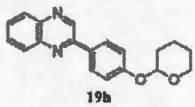
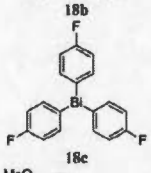
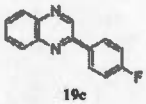
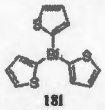
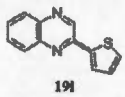
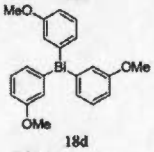
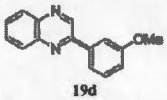
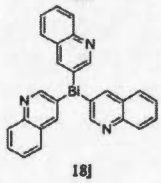
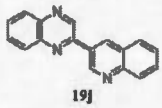
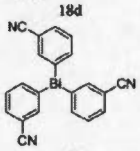
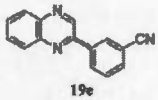
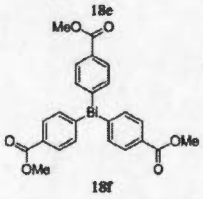
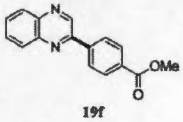
Having established general conditions for the coupling of functionalized organobismuthanes with 2-haloazines and -diazines, we wanted to extend our methodology to the transfer of an aryl fragment that would bear a more reactive functional group such as an aldehyde. This particular functional group is highly reactive and is therefore incompatible with strong organometallic species such as organomagnesium reagents. However, owing to the mild reactivity of the C–Bi bond, we postulated that the aldehyde would be tolerated during the formation and the cross-coupling reaction of the organobismuthane. Only two examples of (formylaryl)bismuthanes have been reported in the literature, but the yields for their synthesis were low, and the species were not used in subsequent coupling reactions.[27]

To test the compatibility of aldehydes with organobismuthanes in the context of a palladium cross-coupling reaction, we sought to prepare a formylphenylbismuth reagent directly from **18g**. The question we asked ourselves was how to liberate the aldehyde without breaking the C–Bi bond. To our great pleasure, tris(3-formylphenyl)bismuthane (**20**) was obtained in 75% yield simply by exposing **18g** to aqueous acidic conditions (Scheme 3). These results show that the C–Bi is strong enough to resist protic conditions. This reaction was performed successfully on a gram scale, and no decomposition was noticed after 1 month upon storing the reagent at room temperature in air. A limited number of organometallic reagents bearing formylaryl groups have been described in the literature,[28,29] and to the best of our knowledge, only three reports of the hydrolysis of acetals directly on the organometallic reagent could be found, those being with germanium,[30] antimony,[31] and mercury.[32]

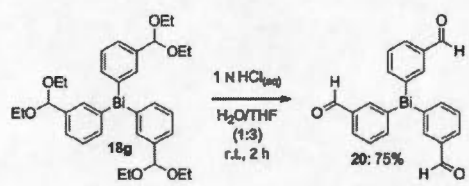
To unequivocally confirm the structure of this new organometallic reagent, compound **20** was recrystallized. X-ray diffraction analysis revealed that the compound is pyramidal and has C–Bi–C angles of 92.02° and C–Bi bond lengths of 2.266 Å (Figure 1). The structure clearly shows the presence of three aryl groups each bearing a formyl moiety.

Table 3. Cross-coupling of functionalized triaryl- and triheteroarylbismuthanes 18a–j with 2-chloroquinoxaline (7a).



Entry	Organobismuthane	Product	Yield [%][a]	Entry	Organobismuthane	Product	Yield [%][a]
1	 18a	 19a	86	7	 18g	 19g	98
2	 18b	 19b	20	8	 18h	 19h	80
3	 18c	 19c	90	9	 18i	 19i	85
4	 18d	 19d	97	10	 18j	 19j	45
5	 18e	 19e	84				
6[b]	 18f	 19f	80				

[a] Yield of isolated pure product. [b] 10 mol-% of $Pd(PPh_3)_4$ and 0.7 equiv. of Ar_3Bi were used.



Scheme 3. Synthesis of tris(3-formylphenyl)bismuthane (20).

We next verified the transferability of the formylphenyl group of **20** by conducting the cross-coupling reaction with pyrazine **7a** under our standard conditions and obtained the corresponding cross-coupling product **21** in 80% isolated yield (Scheme 4).

Isolated examples of cross-coupling reactions leading to the transfer of a formylaryl group on azines and diazines have been reported.[33–36] However, to the best of our knowledge, the only general methods for the coupling of

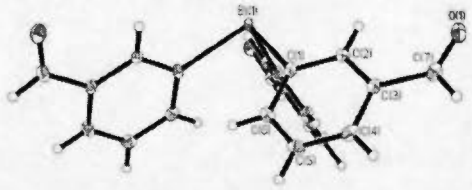
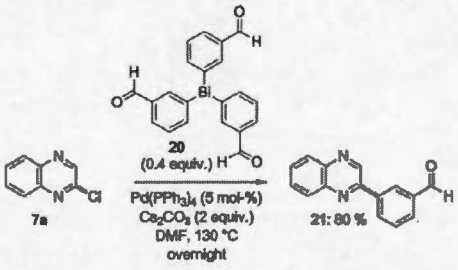


Figure 1. ORTEP diagram of compound **20**. Thermal ellipsoids are shown at the 50% probability level.



Scheme 4. Cross-coupling reaction between (formylphenyl)bismuth **20** and 2-chloroquinoxaline (**7a**).

highly functionalized aryl groups (including formylaryl) are those developed by Knochel that involve organozinc[37] and organoindium reagents.[38] Contrary to organozinc species, organobismuthanes are not moisture-sensitive and can be manipulated in air.

Conclusions

We have developed an efficient protocol for the cross-coupling of functionalized aryl- and heteroarylbismuth reagents with 2-halo(or 2-triflyl)pyridines, -pyrimidines, -pyrazines, and -pyridazines bearing reactive moieties. This method involves shelf-stable organobismuthanes and proceeds under simple conditions to provide the desired coupling products in good to excellent yields. All three aryl groups are transferred from the bismuthane in the course of the coupling process. The coupling on 2,4-dichloropyrimidines is regioselective and affords mainly the monophenyl product resulting from the reaction at the 4-position. We demonstrated that functional group manipulation directly on the organobismuth species is possible and gives access to functionalized aryl groups that are challenging to transfer such as formylaryl groups. The cross-coupling of a formylphenyl group was efficiently accomplished by using our protocol. Studies on the derivatization of organobismuthanes and their use in cross-coupling reactions with other electrophiles are in progress in our laboratory. Results will be reported in due course.

Experimental Section

Typical Procedure for the Cross-Coupling Reaction between Organobismuthanes and 2-Chloro-, 2-Bromo-, and 2-Triflyl(df)azines: In a sealed tube, the 2-halo(2-triflyl)azine or -diazine (0.30 mmol) was dissolved in dry *N,N*-dimethylformamide (4.5 mL). Cesium carbonate (0.60 mmol) was added, followed by tetrakis(triphenylphosphane)palladium (0.015 mmol) and the arylbismuth reagent (0.12 mmol). Argon was bubbled into the reaction mixture for 5 min. The tube was sealed and heated at 130 °C overnight. The reaction mixture was cooled to room temperature, diluted with a saturated aqueous solution of sodium hydrogen carbonate (50 mL), and extracted with ethyl acetate (2× 50 mL). The combined organic phases were washed with a saturated aqueous solution of sodium hydrogen carbonate (2× 50 mL) and brine (2× 50 mL), dried with sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexanes/ethyl acetate) to afford the corresponding product.

CCDC-949485 (for **20**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Experimental details, characterization data, and copies of the ^1H and ^{13}C NMR spectra of all key intermediates and final compounds.

Acknowledgments

This work was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC) and the Université du Québec à Montréal (UQAM). P. P. thanks UQAM for a FARE scholarship. We thank Michel Simard from Université de Montréal for the X-ray analysis of compound **20** and Dr. Alexandre Arnold for assistance with advanced NMR studies.

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ANNEXE D

"PALLADIUM-CATALYZED CROSS-COUPLING REACTION OF FUNCTIONALIZED ARYL- AND HETEROARYLBISMUTHANES WITH 2-HALO(OR 2-TRIFLYL)AZINES AND DIAZINES" SUPPORTING INFORMATION

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Auteurs : Pauline Petiot et Alexandre Gagnon*

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SUPPORTING INFORMATION

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Table of contents:

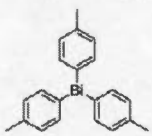
1. General information

All reactions were run under argon atmosphere in non flame dried glassware. Unless otherwise stated, commercial reagents were used without further purification. Grignard reagents were purchased from Aldrich or prepared using conventional methods with metallic magnesium or via Knochel's procedure[1] and were titrated prior use.[2] Triphenylbismuth and anhydrous bismuth chloride 99.999% were purchased from Strem Chemicals. Anhydrous solvents were obtained using a MBRAUN (model MB-SPS 800) encapsulated solvent purification system. The evolution of reactions was monitored by analytical thin-layer chromatography using silica gel 60 F254 precoated plates. Flash chromatography was performed employing 230-400 mesh silica (Silicycle) using the indicated solvent system according to standard techniques.[3] Microwave irradiation was conducted using a Biotage® Initiator microwave system. Melting points were taken on an Electrothermal Mel-TEMP and are uncorrected. Nuclear magnetic resonance spectra (^{1}H, ^{13}C) were recorded on a Bruker Avance-III 300MHz spectrometer. Chemical shifts for ^{1}H-NMR spectra are recorded in parts per millon from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ 7.27 ppm, DMSO δ 2.54 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant J in Hz and integration. Chemical shifts for ^{13}C spectra are recorded in parts per million from tetramethylsilane using the central peak of deuterochloroform (77.00 ppm) as the internal standard. All ^{13}C spectra were obtained with complete proton decoupling. IR spectra were recorded on a Thermo Scientific Nicolet 6700 PT-IR from thin films and are reported in reciprocal centimeters (cm^{-1}). HRMS were performed at Université du Québec à Montréal on Agilent Technologies, LC 1200 Series / 6210 TOF LCMS analyzer using the electrospray (ESI) mode.

2. General procedure for the preparation of triarylbismuthanes

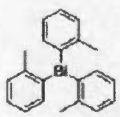
Bismuth chloride (500 mg, 1.6 mmol) was dissolved in anhydrous THF (23 mL) and was cooled to – 10°C (ice-acetone bath). The organomagnesium reagent (5.23 mmol) was slowly added dropwise under argon. The reaction mixture was stirred at room temperature (r.t.) for one hour and heated at 65°C for 30 minutes. After cooling to r.t., the solution was diluted with sat. aq. sodium bicarbonate (100 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic phases were washed with sat. aq. sodium bicarbonate (2 x 100 mL), brine (2 x 100 mL), dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using the indicated solvent system to afford the desired triarylbismuth.

Tris(4-methylphenyl)bismuthine (18a)



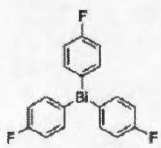
The general procedure was followed on a 1.6 mmol scale starting from $BiCl_3$ and *p*-tolylmagnesium bromide. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford **18a** as a white solid (430 mg, 60%); m.p. 119-120°C. Spectral data was identical to literature compound.[4] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.64 (d, J = 7.8 Hz, 2H), 7.20 (d, J = 7.4 Hz, 2H), 2.32 (s, 3H).

Tris(2-methylphenyl)bismuthine (18b)



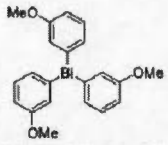
The general procedure was followed on a 1.6 mmol scale starting from $BiCl_3$ and *o*-tolylmagnesium bromide. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford **18b** as a white solid (664 mg, 86%); m.p. 130-131°C. Spectral data was identical to literature compound.[4] ^{1}H-NMR (300 MHz, $CDCl_3$) 7.59 (dd, J = 7.3, 1.0 Hz , 1H), 7.39-7.28 (m, 2H), 7.10 (t, J = 7.3 Hz, 1H), 2.47 (s, 3H).

Tris(4-fluorophenyl)bismuthine (18c)



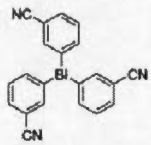
The general procedure was followed on a 1.6 mmol scale starting from $BiCl_3$ and 4-fluorophenyl magnesium bromide. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **18c** as a white solid (615 mg, 80%); m.p. 93-94°C. Spectral data was identical to literature compound.[4] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.64 (dd, J = 8.4, 2.0 Hz, 2H), 7.08 (t, J = 9.2 Hz, 2H).

Tris(3-methoxyphenyl)bismuthine (18d)



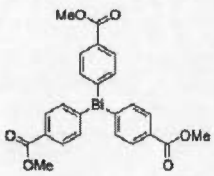
The general procedure was followed on a 1.6 mmol scale starting from $BiCl_3$ and 3-methoxyphenyl magnesium bromide. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford **18d** as a yellow solid (732 mg, 86%); m.p. 95-100°C. Spectral data was identical to literature compound.[4] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37-7.31 (m, 3H), 6.85-6.82 (m, 1H), 3.72 (s, 3H).

Tris(3-cyanophenyl)bismuthine (18e)



Preparation of 3-benzonitrile magnesium bromide using Knochel's procedure[1]*:* A solution of *i*-PrMgCl•LiCl (4.6 mL, 6.0 mmol, 1.3M in THF) was cooled to –20°C, and 3-bromobenzonitrile (1.0 g, 5.5 mmol) was added. The reaction mixture was stirred for 30 min at –20°C. The general procedure was then followed on a 1.65 mmol scale starting from bismuth chloride. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford **18e** as a yellow oil (389 mg, 20%); R_f 0.11 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.94 (dt, J = 7.4, 1.1 Hz, 1H), 7.62 (dt, J = 7.7, 1.4 Hz, 1H), 7.53 (t, J = 7.5 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 157.1, 141.4, 140.5, 132.0, 131.3, 118.7, 115.2; IR (neat) 3407, 3047, 2230, 1545, 1393; HRMS (ESI) calcd for $C_{21}H_{12}BiN_3$: 515.0835, found $(M+H)^+$ 516.0908.

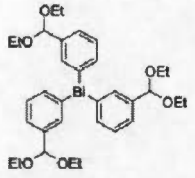
Tris(4-carbomethoxyphenyl)bismuthine (18f)



Preparation of (4-carbomethoxyphenyl)magnesium bromide using Knochel's procedure[1]*:* A solution of *i*-PrMgCl•LiCl (21.2 mL, 16.8 mmol, 1.3M in THF) was cooled to –50°C, and methyl 4-bromobenzoate (4.0 g, 15 mmol) was added. The reaction mixture was stirred for 30 min at –50°C. The general procedure was then followed on a 4.5 mmol scale starting from bismuth chloride. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford **18f** as a yellow solid (1.3 g, 60%). Spectral data was identical to literature compound.[4] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 8.2 Hz, 2H), 7.79 (d, J = 8.1 Hz, 2H), 3.89 (s, 3H).

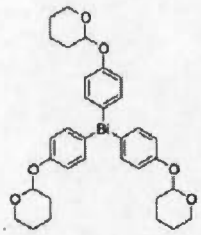
Tris(3-(diethoxymethyl)phenyl)bismuthine (18g)

The general procedure was followed on a 6.4 mmol scale starting from $BiCl_3$ and 3-(benzaldehyde diethylacetal)magnesium bromide. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford **18g** as a yellow oil (4.2 g, 88%); R_f 0.69 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.66 (d, J = 7.1 Hz, 1H), 7.44-7.33 (m, 2H), 5.44 (s, 1H), 3.62-3.43 (m, 4H), 1.18 (t, J = 7.1 Hz, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 155.2, 140.5, 137.5, 135.7, 130.3, 126.1, 101.7, 61.0, 15.2; IR



(neat) 3647, 2983, 2874, 1699, 1433, 1108, 1045; HRMS (ESI) calcd for $C_{33}H_{45}BiO_6$: 746.3020, found $(M+Na)^+$ 769.2912.

Tris(4-(tetrahydro-2H-pyran-2-yloxy)phenyl)bismuthine (18h)

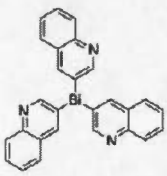


The general procedure was followed on a 1.6 mmol scale starting from $BiCl_3$ and 4-(2-tetrahydro-2H-pyranoxy)phenylmagnesium bromide. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford **18h** as a white solid (650 mg, 55%); R_f 0.44 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 8.5 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H), 5.55 (t, J = 3.2 Hz, 1H), 4.10-4.03 (m, 1H), 3.78-3.73 (m, 1H), 2.20-2.12 (m, 1H), 2.01-1.97 (m, 2H), 1.84-1.72 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 156.9, 138.9, 118.8, 96.4, 62.3, 30.5, 25.4, 19.0; IR (neat) 3020, 2941, 2871, 1580, 1485, 1232.

Tris(2-thienyl)bismuthine (18i)

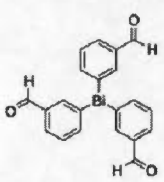
The general procedure was followed on a 1.6 mmol scale starting from $BiCl_3$ and 2-thienylmagnesium bromide. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford **18i** as a yellow solid (387 mg, 53%). Spectral data was identical to literature compound.[4] T. decomp 250°C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.69 (dd, J = 4.8, 0.7 Hz, 1H), 7.45 (dd, J = 3.3, 0.8 Hz, 1H), 7.19 (dd, J = 4.8, 1.4 Hz, 1H).

Tris(3-quinolinyl)bismuthine (18j)



The general procedure was followed on a 1.6 mmol scale starting from $BiCl_3$ and 3-quinolinylmagnesium bromide. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford **18j** as a colorless oil (743 mg, 80%); R_f 0.61 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.90 (d, J = 2.3 Hz, 1H), 8.31 (d, J = 2.2 Hz, 1H), 8.09 (d, J = 9.0 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.73 (dt, J = 6.9, 1.1 Hz, 1H), 7.57 (dt, J = 8.2, 1.5 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 150.8, 145.8, 136.7, 129.3, 129.1, 128.6, 127.1, 126.5, 116.7; IR (neat) 3059, 1581, 1498, 1311, 1071.

Tris(3-formylphenyl)bismuthine (20)



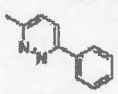
H_2O (26 mL) and HCl 1N (10 mL) were added at room temperature to a stirred solution of tris(3-(diethoxymethyl)phenyl)bismuthane (2.0 g, 2.8 mmol) (**18g**) in THF (50 mL). The reaction mixture was stirred for 1h and then diluted with ethyl acetate (50 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (50 mL) and sat. aq.

NaCl (3 x 50 mL), dried over $Na_2S_2O_4$, filtered and concentrated under reduced pressure. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford **20** as a white solid (991 mg, 75%); m.p. 125°C; R_f 0.29 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.97 (s, 1H), 8.26 (s, 1H), 7.96 (d, J = 7.3 Hz, 1H), 7.86 (dt, J = 7.7, 1.3 Hz, 1H), 7.58 (t, J = 7.5 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 192.4, 156.1, 143.50, 138.4, 138.0, 131.5, 129.9; IR (neat) 3032, 2839, 2732, 1695, 1575, 1553, 1382, 1193; HRMS (ESI) calcd for $C_{21}H_{15}BiO_3$: 524.0825, found $(M+H)^+$ 525.0898.

3. General procedure for the cross-coupling reaction between triarylbismuthanes and 2-chloro, 2-bromo, and 2-triflyl azines and diazines

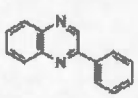
Compounds **6**, **11a-11d**, **12a**, **13a-13m**, **14a**, **16**, **17**, **19a-19j** and **21** were prepared according to the following procedure: In a sealed tube, the starting bromide, chloride or triflate (0.30 mmol) was dissolved in *N,N*-dimethylformamide (4.5 mL). Cesium carbonate (198 mg, 0.60 mmol) was added, followed by tetrakis(triphenylphosphine)palladium (18 mg, 0.015 mmol) and triarylbismuth or triheteroarylbismuth reagent (60 mg, 0.12 mmol). Argon was bubbled in the reaction mixture for 5 minutes. The tube was sealed and heated at 130°C for 18h. The reaction mixture was cooled to r.t., diluted with sat. aq. sodium bicarbonate (50 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic phases were washed with sat. aq. sodium bicarbonate (2 x 50 mL), brine (2 x 50 mL), dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using hexanes/ethyl acetate as the eluent to afford the corresponding product.

3-Methyl-6-phenylpyridazine (6)



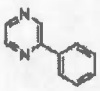
The general procedure was followed on a 0.39 mmol scale starting from 3-chloro-6-methylpyridazine (**4**). The crude material was purified on silica gel (10% EtOAc/hexanes) to afford **6** as a white solid (47 mg, 72%); m.p. 56-58 °C. Spectral data was identical to literature compound.[5] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.05 (dd, J = 8.1, 1.8 Hz, 2H), 7.73 (d, J = 8.7 Hz, 1H), 7.50-7.46 (m, 3H), 7.37 (d, J = 8.7 Hz, 1H), 2.74 (s, 3H).

2-Phenylquinoxaline (11a)



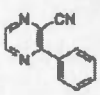
The general procedure was followed on a 0.31 mmol scale starting from 2-chloroquinoxaline (**7a**). The crude material was purified on silica gel (2.5% EtOAc/hexanes) to afford **11a** as a yellow solid (57 mg, 91%); m.p. 78-79°C. Spectral data was identical to literature compound.[5] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.31 (s, 1H), 8.20-8.10 (m, 4H), 7.79-7.69 (m, 2H), 7.58-7.47 (m, 3H).

2-Phenylpyrazine (11b)



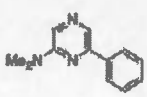
The general procedure was followed on a 0.44 mmol scale starting from 2-chloropyrazine (**7b**). The crude material was purified on silica gel (5% EtOAc/hexanes) to afford **11b** as a white solid (55 mg, 81%); m.p. 72-73°C. Spectral data was identical to literature compound.[6] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.61 (t, J = 2.3 Hz, 1H), 8.49 (d, J = 2.5 Hz, 1H), 8.01 (dd, J = 8.1, 1.9 Hz, 2H), 7.54-7-43 (m, 3H).

2-Cyano-3-phenylpyrazine (11c)



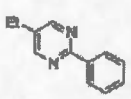
The general procedure was followed on a 0.36 mmol scale starting from 2-chloro-3-cyanopyrazine (**7c**). The crude material was purified on silica gel (5% EtOAc/hexanes) to afford **11c** as a colorless oil (40 mg, 62%); R_f 0.39 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.84 (d, J = 2.3 Hz, 1H), 8.65 (d, J = 2.3 Hz, 1H), 8.00-7.98 (m, 2H), 7.59-7.57 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 157.2, 146.6, 143.1, 134.5, 131.2, 129.2, 128.1, 116.5; IR (neat) 3060, 2919, 2850, 2235, 1547; HRMS (ESI) calcd for $C_{11}H_7N_3$: 181.0640, found $(M+H)^+$ 182.0718.

2-(*N*,*N*-dimethylamino)-6-phenylpyrazine (11d)



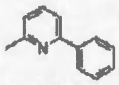
The general procedure was followed on a 0.32 mmol scale starting from 2-chloro-6-(*N*,*N*-dimethylamino)pyrazine (**7d**). The crude material was purified on silica gel (5% EtOAc/hexanes) to afford **11d** as a yellow oil (45 mg, 72%); R_f 0.22 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.04-8.01 (m, 2H), 7.97 (s, 1H), 7.50-7.38 (m, 3H), 3.20 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 154.3, 149.2, 137.5, 129.2, 128.7, 128.4, 128.0, 126.8, 37.5; IR (neat) 3037, 2919, 2895, 1603, 1529, 1426; HRMS (ESI) calcd for $C_{12}H_{13}N_3$: 199.1109, found $(M+H)^+$ 200.1257.

5-Ethyl-2-phenylpyrimidine (12a)



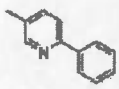
The general procedure was followed on a 0.35 mmol scale starting from 2-chloro-5-ethylpyrimidine (**8a**). The crude material was purified on silica gel (1.5% EtOAc/hexanes) to afford **12a** as a colorless oil (40 mg, 62%); R_f 0.64 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.65 (s, 2H), 8.42-8.39 (m, 2H), 7.50-7.47 (m, 3H), 2.67 (q, J = 7.7 Hz, 2H), 1.31 (t, J = 7.6 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 162.8, 156.8, 137.8, 134.3, 130.5, 128.7, 128.0, 23.6, 15.1; IR (neat) 3015, 2965, 2928, 1586, 1427.

2-Methyl-6-phenylpyridine (13a)



The general procedure was followed on a 0.39 mmol scale starting from 2-chloro-6-methylpyridine (**9a**). The crude material was purified on silica gel (5% EtOAc/hexanes) to afford **13a** as a colorless oil (43 mg, 65%). Spectral data was identical to literature compound.[7] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.99 (dd, J = 8.5, 1.6 Hz, 2H), 7.63 (t, J = 7.7 Hz, 1H), 7.53-7.34 (m, 4H), 7.15-7.05 (m, 1H), 2.64 (s, 3H).

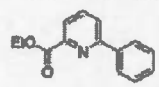
3-Methyl-6-phenylpyridine (13b)



The general procedure was followed on a 0.29 mmol scale starting from 2-bromo-5-methylpyridine (**9b**). The crude material was purified on silica gel (5% EtOAc/hexanes) to afford **13b** as a colorless oil (43 mg, 90%). Spectral data was identical to literature compound.[8]

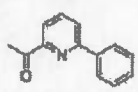
The general procedure was also followed on a 0.21 mmol scale starting from 5-methyl-2-trifluoromethylsulfonatepyridine (**9i**). The crude material was purified on silica gel (5% EtOAc/hexanes) to afford **13b** as a colorless oil (23 mg, 66%). Spectral data was identical to literature compound.[8] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.97 (dt, J = 7.0, 1.6 Hz, 2H), 7.63 (d, J = 8.1 Hz, 1H), 7.55 (dd, J = 8.1, 1.8 Hz, 1H), 7.49-7.36 (m, 3H), 2.36 (s, 3H).

Ethyl 6-phenylpyridine-2-carboxylate (13c)



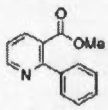
The general procedure was followed on a 0.22 mmol scale starting from ethyl 6-bromo-2-pyridine carboxylate (**9c**). The crude material was purified on silica gel (2.5% EtOAc/hexanes) to afford **13c** as a yellow solid (24 mg, 50%); m.p. 53-55°C. Spectral data was identical to literature compound.[9] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.09-8.01 (m, 3H), 7.91-7.85 (m, 2H), 7.52-7.40 (m, 3H), 4.48 (q, J = 7.1 Hz, 2H), 1.47 (t, J = 7.1 Hz, 3H).

2-Acetyl-6-phenylpyridine (13d)



The general procedure was followed on a 0.25 mmol scale starting from 2-acetyl-6-bromopyridine (**9d**). The crude material was purified on silica gel (5% EtOAc/hexanes) to afford **13d** as a yellow solid (46 mg, 76%); m.p. 59-61°C. Spectral data was identical to literature compound.[10] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.10 (dt, J = 6.7, 1.6 Hz, 2H), 7.98 (dd, J = 7.1, 1.7 Hz, 1H), 7.94-7.85 (m, 2H), 7.54-7.46 (m, 3H), 2.83 (s, 3H).

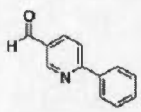
Methyl 2-phenylpyridine-3-carboxylate (13e)



The general procedure was followed on a 0.23 mmol scale starting from methyl 2-bromopyridine-3-carboxylate (**9e**). The crude material was purified on silica gel (10% EtOAc/hexanes) to afford **13e** as a yellow oil (24 mg, 50%).

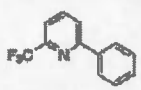
The general procedure was also followed on a 0.29 mmol scale starting from methyl 2-chloropyridine-3-carboxylate (**9f**). The crude material was purified on silica gel (5% EtOAc/hexanes) to afford **13e** as a yellow oil (26 mg, 42%); R_f 0.37 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.78 (dd, J = 3.8, 1.7 Hz, 1H), 8.10 (dd, J = 7.8, 1.7 Hz, 1H), 7.56-7.53 (m, 2H), 7.47-7.42 (m, 3H), 7.33 (dd, J = 7.8, 4.8 Hz, 1H), 3.69 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.7, 158.9, 151.4, 140.1, 138.0, 128.8, 128.6, 128.3, 127.1, 121.7, 52.5; IR (neat) 3025, 2950, 1725, 1581, 1426, 1282; HRMS (ESI) calcd for $C_{13}H_{11}NO_2$: 213.0790, found $(M+H)^+$ 214.0972.

3-Carboxaldehyde-6-phenylpyridine (13g)



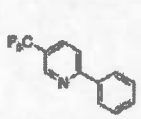
The general procedure was followed on a 0.35 mmol scale starting from 6-chloro-3-carboxaldehydepyridine (**9g**). The crude material was purified on silica gel (5% EtOAc/hexanes) to afford **13g** as a white solid (50 mg, 80%); m.p. 58-59°C. Spectral data was identical to literature compound.[11] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.13 (s, 1H), 9.13 (d, J = 1.9 Hz, 1H), 8.19 (dd, J = 8.3, 1.2 Hz, 1H), 8.09-8.06 (m, 2H), 7.89 (d, J = 8.3 Hz, 1H), 7.54-7.49 (m, 3H).

2-Phenyl-6-(trifluoromethyl)pyridine (13h)



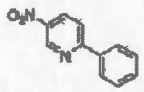
The general procedure was followed on a 0.28 mmol scale starting from 2-chloro-6-trifluoromethylpyridine (**9h**). The crude material was purified on silica gel (2% EtOAc/hexanes) to afford **13h** as a yellow solid (52 mg, 85%); m.p. 50-55°C; R_f 0.71 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.09 (dd, J = 8.2, 1.8 Hz, 2H), 7.91 (d, J = 4.1 Hz, 2H), 7.64-7.58 (m, 1H), 7.53-7.46 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.0, 138.2, 137.9, 129.9, 129.1, 127.3, 123.6, 122.9, 118.6; IR (neat) 3330, 2922, 2831, 1596, 1462, 1451, 1344; HRMS (ESI) calcd for $C_{12}H_8F_3N$: 223.0609, found $(M+H)^+$ 224.0689.

2-Phenyl-5-trifluoromethylpyridine (13j)



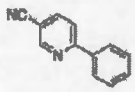
The general procedure was followed on a 0.17 mmol scale starting from 2-trifluoromethylsulfonate-5-trifluoromethylpyridine (**9j**). The crude material was purified on silica gel (2.5% EtOAc/hexanes) to afford **13j** as a colorless oil (30 mg, 80%). Spectral data was identical to literature compound.[12] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.03 (dd, J = 8.0, 2.0 Hz, 2H), 7.98 (dd, J = 8.4, 1.9 Hz, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.54-7.47 (m, 3H).

3-Nitro-6-phenylpyridine (13k)



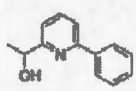
The general procedure was followed on a 0.25 mmol scale starting from 2-bromo-5-nitropyridine (**9k**). The crude material was purified on silica gel (2.5% EtOAc/hexanes) to afford **13k** as a yellow solid (21 mg, 45%); m.p. 119-121°C. Spectral data was identical to literature compound.[13] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.49 (d, J = 2.3 Hz, 1H), 8.53 (dd, J = 8.8, 2.6 Hz, 1H), 8.09 (dd, J = 7.5, 3.7 Hz, 2H), 7.85 (d, J = 8.9 Hz, 1H), 7.54-7.52 (m, 3H).

3-Cyano-6-phenylpyridine (13l)



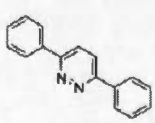
The general procedure was followed on a 0.36 mmol scale starting from 6-chloro-3-pyridinecarbonitrile (**9l**). The crude material was purified on silica gel (2.5% EtOAc/hexanes) to afford **13l** as a white solid (40 mg, 62%); m.p. 95-100°C; R_f 0.48 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.93 (dd, J = 2.1, 0.7 Hz, 1H), 8.06-8.00 (m, 2H), 7.98 (dd, J = 8.3, 2.2 Hz, 1H), 7.83 (dd, J = 8.4, 0.8 Hz, 1H), 7.55-7.49 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 160.6, 152.6, 140.0, 137.5, 130.7, 129.2, 127.5, 120.1, 117.1, 108.0; IR (neat) 3051, 3047, 2238, 1589, 1469, 1444, 1376; HRMS (ESI) calcd for $C_{12}H_8N_2$: 180.0687, found $(M+H)^+$ 181.0766.

α-Methyl-6-phenyl-2-pyridinemethanol (13m)



The general procedure was followed on a 0.25 mmol scale starting from 1-(6-bromo-2-pyridinyl)ethanol (**9m**). The crude material was purified on silica gel (2.5% EtOAc/hexanes) to afford **13m** as a yellow oil (13 mg, 26%). Spectral data was identical to literature compound.[14] ^{1}H-NMR (300 MHz, $CDCl_3$) 8.02 (dd, J = 8.4, 1.7 Hz, 2H), 7.77 (t, J = 7.7 Hz, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.52-7.43 (m, 3H), 7.21 (d, J = 7.7 Hz, 1H), 4.95-4.93 (m, 1H), 4.78-4.77 (m, 1H), 1.56 (d, J = 6.5 Hz, 3H).

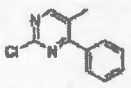
3,6-Diphenylpyridazine (14a)



The general procedure was followed on a 0.25 mmol scale starting from 3-chloro-6-phenylpyridazine (**10a**). The crude material was purified on silica gel (2.5% EtOAc/hexanes) to afford **14a** as a yellow solid (53 mg, 90%); m.p. 221-223°C. Spectral data was identical to literature compound.[15] ^{1}H-NMR (300 MHz, $CDCl_3$) 8.17 (dd, J = 8.2, 1.8 Hz, 4H), 7.94 (s, 2H), 7.58-7.51 (m, 6H).

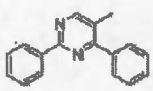
2-Chloro-5-methyl-4-phenylpyrimidine (16) and 2,4-Diphenyl-5-methylpyrimidine (17)

The general procedure was followed on a 0.31 mmol scale starting from 2,4-dichloro-5-methylpyrimidine (**15**). The crude material was purified on silica gel (5% EtOAc/hexanes) to afford **16** as a white solid (39 mg, 65%) and **17** as a white solid (10 mg, 15%).

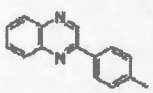


2-Chloro-5-methyl-4-phenylpyrimidine (**16**): R_f 0.47 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.63-7.60 (m, 2H), 7.50-7.47 (m, 3H), 2.38 (s, 3H); nOe experiment: irradiation of the signal at 2.38 ppm yielded nOe transfers to peaks at 8.48 and 7.61 ppm. ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.1, 161.3, 159.1, 136.7, 130.1, 129.0, 128.6, 126.8, 16.7; IR (neat) 3006, 2985, 2926, 1555, 1442, 1436.

2,4-Diphenyl-5-methylpyrimidine (**17**): R_f 0.59 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.52-8.48 (m, 2H), 7.75 (dd, J = 8.0, 2.1 Hz, 2H), 7.57-7.47 (m, 6H), 2.43 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 164.9, 162.6, 159.2, 138.5, 137.8, 130.3, 129.3, 129.2, 128.5, 128.4, 128.1, 125.6, 17.1.

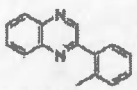


2-(4-Methylphenyl)quinoxaline (19a)



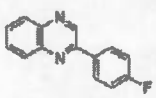
The general procedure was followed on a 0.23 mmol scale starting from 2-chloroquinoxaline (**7a**). The crude material was purified on silica gel (2.5% EtOAc/hexanes) to afford **19a** as a yellow solid (58 mg, 86%); m.p. 92-93°C. Spectral data was identical to literature compound.[16] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.15-8.08 (m, 4H), 7.78-7.68 (m, 2H), 7.34 (d, J = 8.1 Hz, 2H), 2.43 (s, 3H).

2-(2-Methylphenyl)quinoxaline (19b)



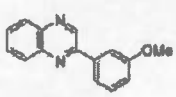
The general procedure was followed on a 0.23 mmol scale starting from 2-chloroquinoxaline (**7a**). The crude material was purified on silica gel (5% EtOAc/hexanes) to afford **19b** as a yellow solid (9 mg, 20%); m.p. 91-92°C. Spectral data was identical to literature compound.[17] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.18-8.15 (m, 2H), 7.84-7.79 (m, 2H), 7.59-7.54 (m, 1H), 7.42-7.34 (m, 3H), 2.48 (s, 3H).

2-(4-Fluorophenyl)quinoxaline (19c)



The general procedure was followed on a 0.23 mmol scale starting from 2-chloroquinoxaline (**7a**). The crude material was purified on silica gel (2.5% EtOAc/hexanes) to afford **19c** as a white solid (61 mg, 90%); m.p. 120-122°C. Spectral data was identical to literature compound.[18] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.58-7.54 (m, 2H), 7.51-7.46 (m, 2H), 7.17-7.07 (m, 2H), 6.61 (t, J = 8.7 Hz, 2H).

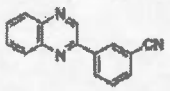
2-(3-Methoxyphenyl)quinoxaline (19d)



The general procedure was followed on a 0.23 mmol scale starting from 2-chloroquinoxaline (**7a**). The crude material was purified on silica gel (5%

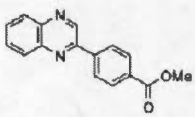
EtOAc/hexanes) to afford **19d** as a yellow solid (70 mg, 97%); m.p. 87-88°C. Spectral data was identical to literature compound.[17] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.17-8.09 (m, 2H), 7.79-7.70 (m, 4H), 7.45 (t, J = 8.1 Hz, 1H), 7.04 (dd, J = 8.2, 3.2 Hz, 1H), 3.92 (s, 3H).

2-(3-Cyanophenyl)quinoxaline (19e)



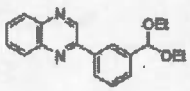
The general procedure was followed on a 0.23 mmol scale starting from 2-chloroquinoxaline (**7a**). The crude material was purified on silica gel (5% EtOAc/hexanes) to afford **19e** as a white solid (45 mg, 84%); m.p. 155-160°C; R_f 0.28 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.31 (s, 1H), 8.53 (s, 1H), 8.40 (dt, J = 8.0, 1.3 Hz, 1H), 8.17-8.12 (m, 2H), 7.85-7.77 (m, 3H), 7.67 (t, J = 7.8 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 149.3, 142.5, 142.2, 142.0, 138.0, 133.3, 131.5, 131.2, 130.9, 130.4, 130.0, 129.8, 129.3, 118.4, 113.6; IR (neat) 3058, 2923, 2846, 2230, 1546; HRMS (ESI) calcd for $C_{15}H_9N_3$: 231.0796, found $(M+H)^+$ 232.0843.

2-(4-(Carboxymethyl)phenyl)quinoxaline (19f)



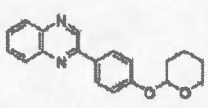
The general procedure was followed on a 0.23 mmol scale starting from 2-chloroquinoxaline (**7a**). The crude material was purified on silica gel (5% EtOAc/hexanes) to afford **19f** as a yellow solid (63 mg, 80%); m.p. 141-143°C. Spectral data was identical to literature compound.[19] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.27-8.17 (m, 3H), 8.16-8.09 (m, 3H), 7.81-7.72 (m, 2H), 3.95 (s, 3H).

2-(2-(diethoxymethyl)quinoxaline (19g)



The general procedure was followed on a 0.23 mmol scale starting from 2-chloroquinoxaline (**7a**). The crude material was purified on silica gel (2% EtOAc/hexanes) to afford **19g** as a yellow oil (70 mg, 98%); R_f 0.47 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.29 (s, 1H), 8.17-8.09 (m, 3H), 7.79-7.70 (m, 2H), 7.64 (d, J = 7.7 Hz, 1H), 7.56 (t, J = 7.6 Hz, 1H), 3.73-3.54 (m, 4H), 1.27 (t, J = 7.1 Hz, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 151.8, 144.3, 143.5, 142.3, 141.6, 140.3, 136.8, 130.3, 129.7, 129.6, 129.2, 128.6, 127.6, 125.9, 101.4, 61.3, 15.3; IR (neat) 3062, 2969, 2921, 2873, 1542, 1186, 1002; HRMS (ESI) calcd for $C_{19}H_{20}N_2O_2$: 308.1525, found $(M+H)^+$ 309.1579.

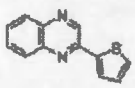
2-(2-(tetrahydro-2H-pyran-2-yloxy)quinoxaline (19h)



The general procedure was followed on a 0.23 mmol scale starting from 2-chloroquinoxaline (**7a**). The crude material was purified on silica gel (2% EtOAc/hexanes) to afford **19h** as a yellow solid (65 mg, 80%); R_f 0.43 (20%

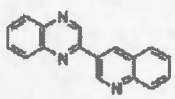
EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.20-8.10 (m, 4H), 7.81-7.70 (m, 2H), 7.30-7.25 (m, 2H), 5.57 (t, J = 3.1 Hz, 1H), 3.99-3.91 (m, 1H), 3.70-3.64 (m, 1H), 2.13-2.05 (m, 1H), 1.97-1.93 (m, 2H), 1.81-1.62 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.9, 151.5, 143.2, 142.4, 141.3, 130.1, 130.0, 129.1, 129.5, 128.9, 117.0, 96.2, 62.0, 30.2, 25.2, 18.6; IR (neat) 3015, 2941, 1604.

2-(2-thienyl)quinoxaline (19i)



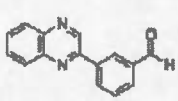
The general procedure was followed on a 0.23 mmol scale starting from 2-chloroquinoxaline (**7a**). The crude material was purified on silica gel (5% EtOAc/hexanes) to afford **19i** as an off white solid (55 mg, 85%); m.p. 117-120°C. Spectral data was identical to literature compound.[20] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.06 (dt, J = 8.2, 1.5 Hz, 2H), 7.84 (dd, J = 3.8, 1.0 Hz, 1H), 7.75-7.65 (m, 2H), 7.53 (dd, J = 3.4, 1.0 Hz, 1H), 7.19 (dd, J = 5.1, 3.8 Hz, 1H).

2-(2-(3-quinolinyl)quinoxaline (19j)



The general procedure was followed on a 0.23 mmol scale starting from 2-chloroquinoxaline (**7a**). The crude material was purified on silica gel (5% EtOAc/hexanes) to afford **19j** as a yellow solid (26 mg, 45%); m.p. 214-215°C. Spectral data was identical to literature compound.[21] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.87 (d, J = 2.2 Hz, 2H), 8.23 (d, J = 2.5 Hz, 2H), 8.04 (d, J = 8.4 Hz, 2H), 7.71-7.66 (m, 4H), 7.52 (dt, J = 6.9, 1.1 Hz, 1H).

2-(2-(3-formylphenyl)quinoxaline (21)



The general procedure was followed on a 0.23 mmol scale starting from 2-chloroquinoxaline (**7a**). The crude material was purified on silica gel (2% EtOAc/hexanes) to afford **21** as a yellow solid (43 mg, 80%); m.p. 120-123°C; R_f 0.36 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.15 (s, 1H), 9.36 (s, 1H), 8.70 (s, 1H), 8.46 (d, J = 7.8 Hz, 1H), 8.12 (dt, J = 8.5, 2.1 Hz, 2H), 8.00 (d, J = 7.6 Hz, 1H), 7.80-7.69 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 191.9, 150.3, 142.9, 142.2, 141.9, 137.8, 137.2, 133.2, 131.0, 130.7, 130.2, 129.9, 129.7, 129.2, 128.8; IR (neat) 3054, 2811, 2726, 1700, 1584, 1538, 1179; HRMS (ESI) calcd for $C_{15}H_{10}N_2O$: 234.0793, found $(M+H)^+$ 235.083

4. References

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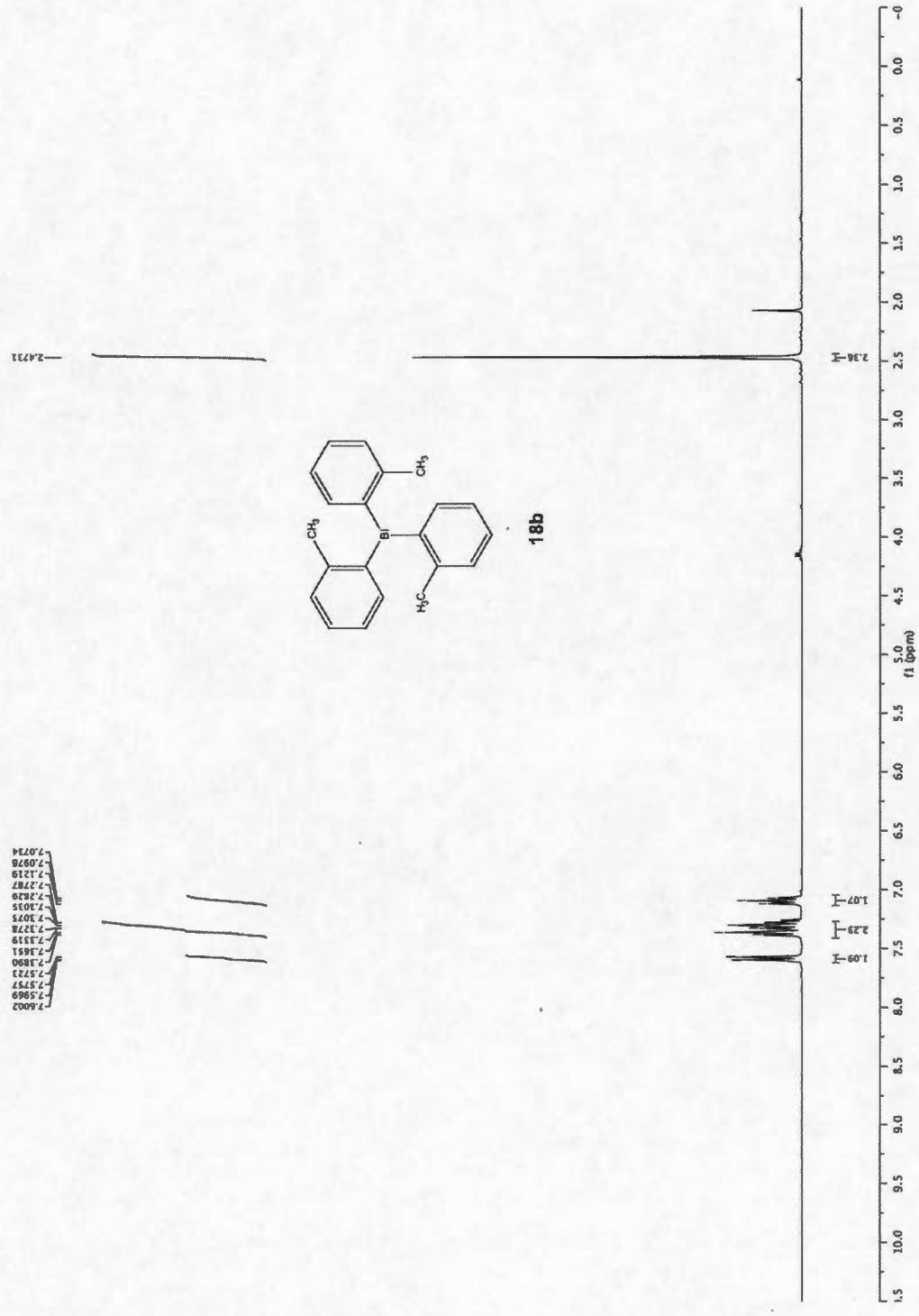
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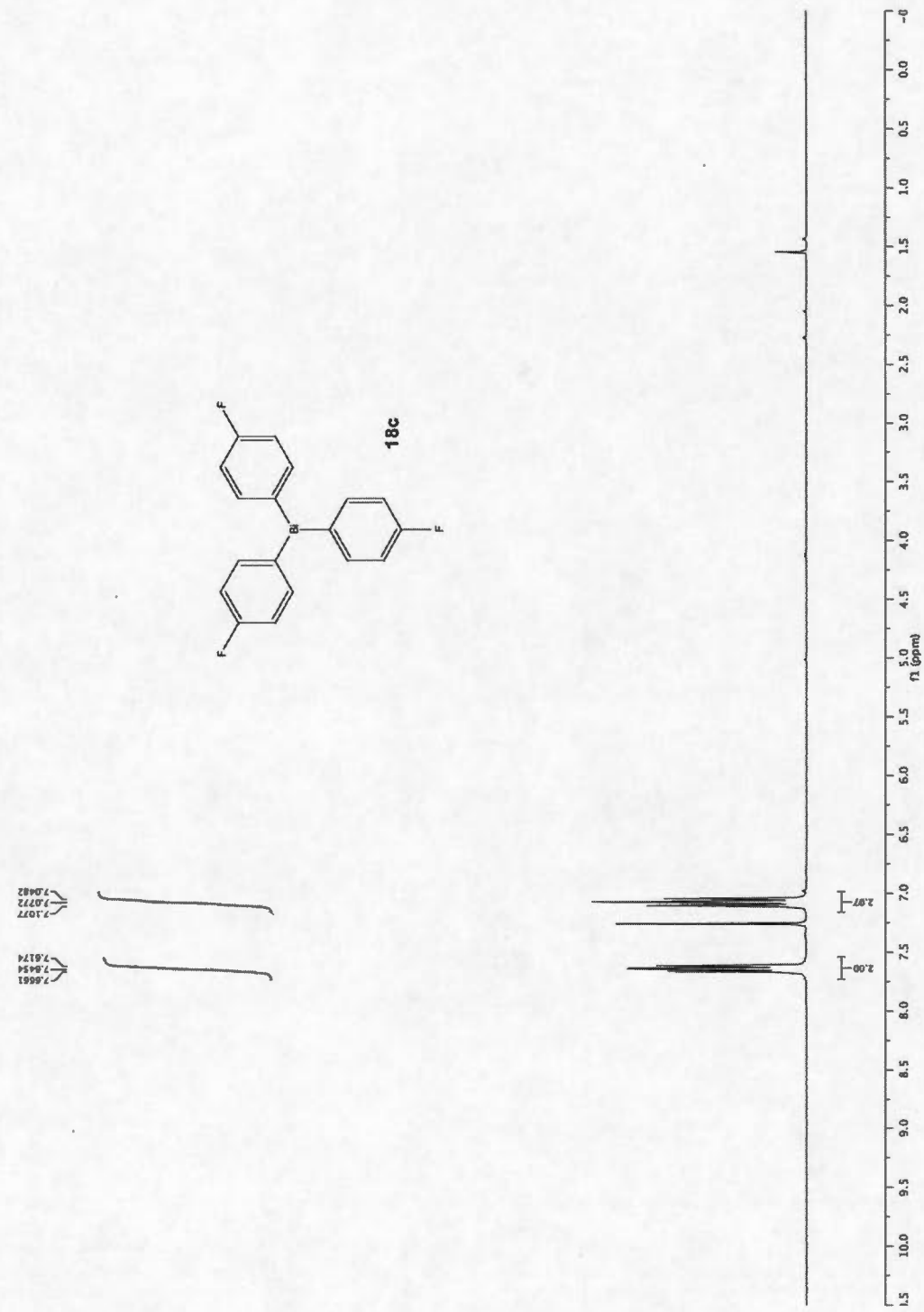
f1 (ppm)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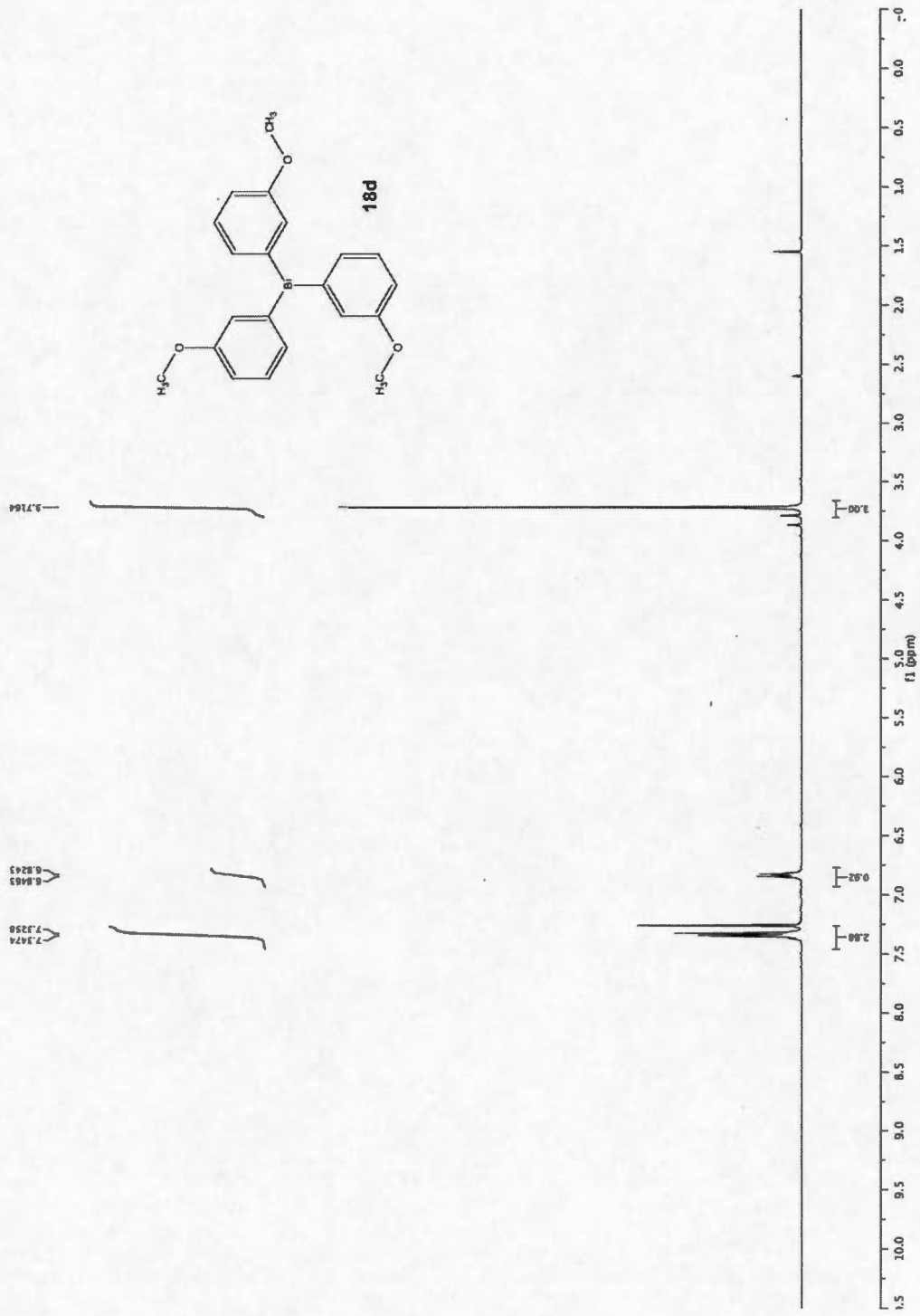
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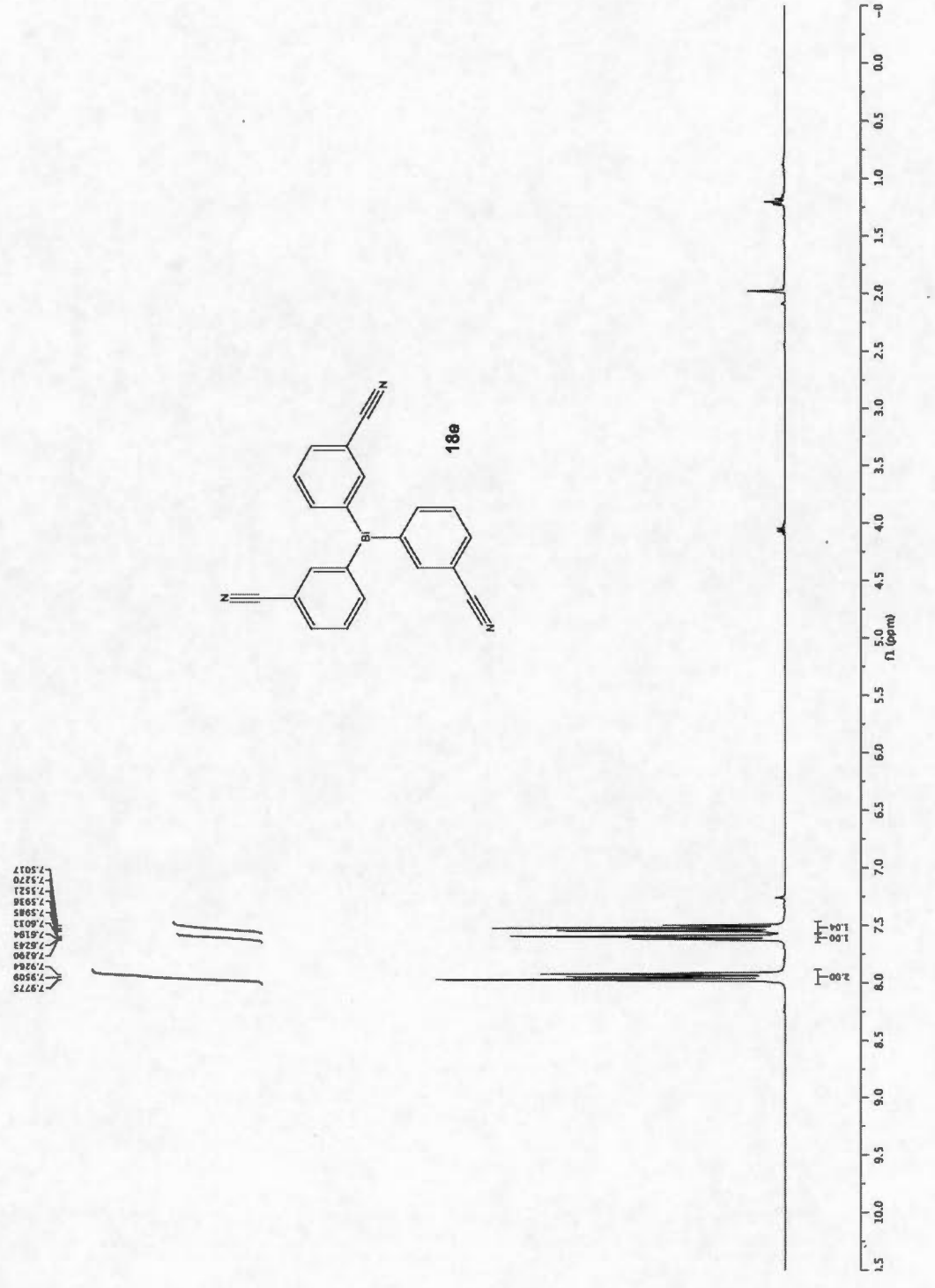
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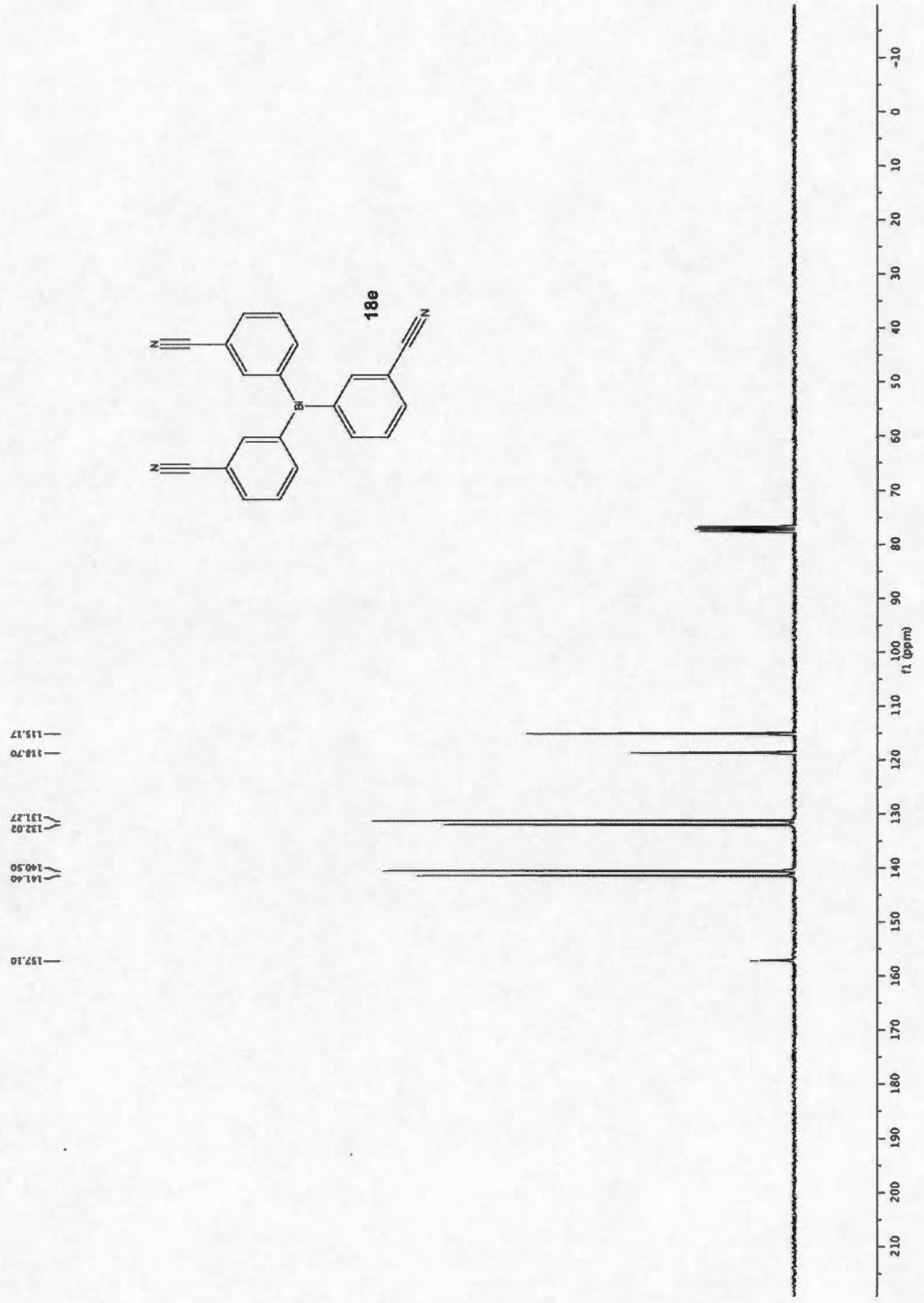
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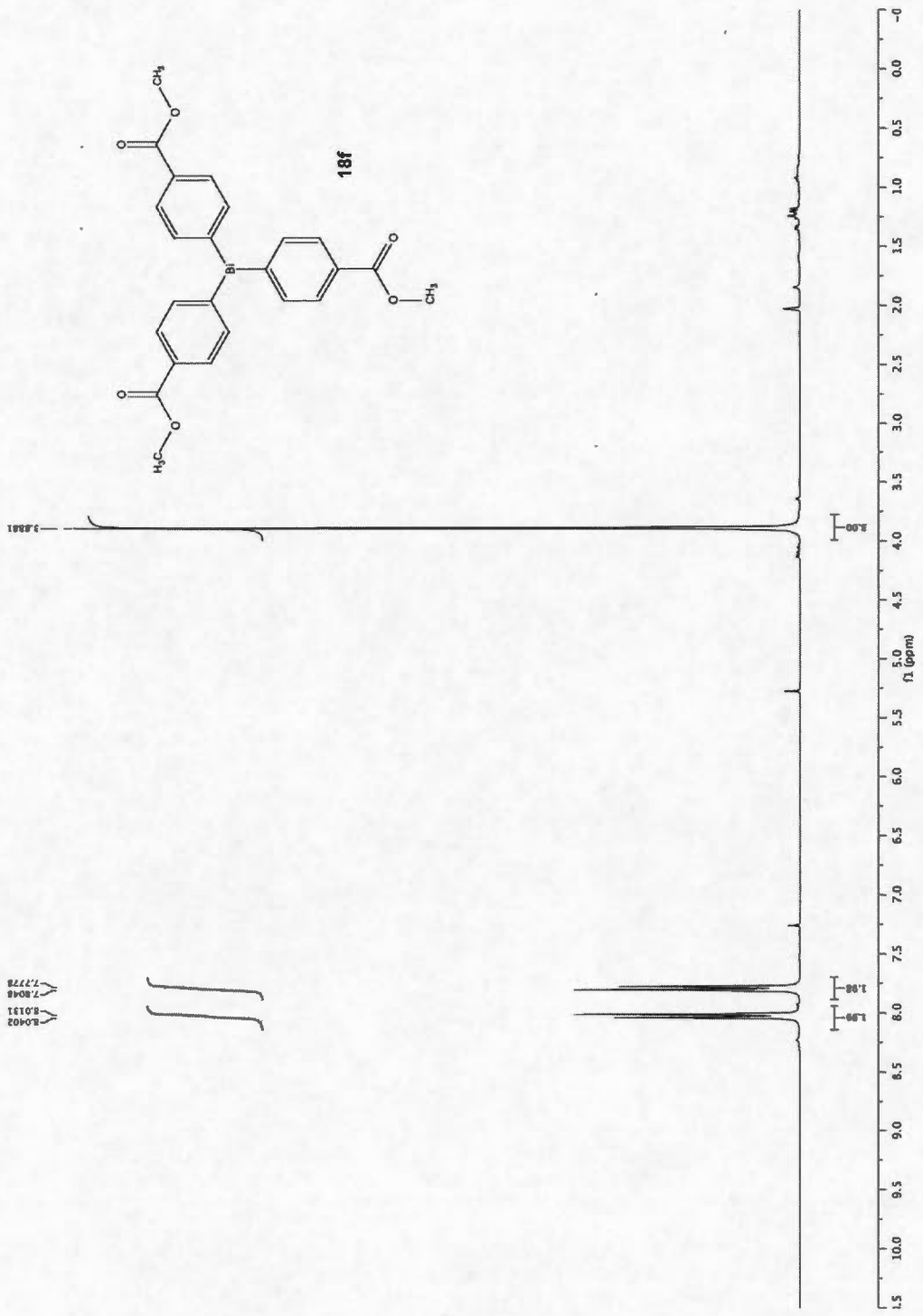
f1 (ppm)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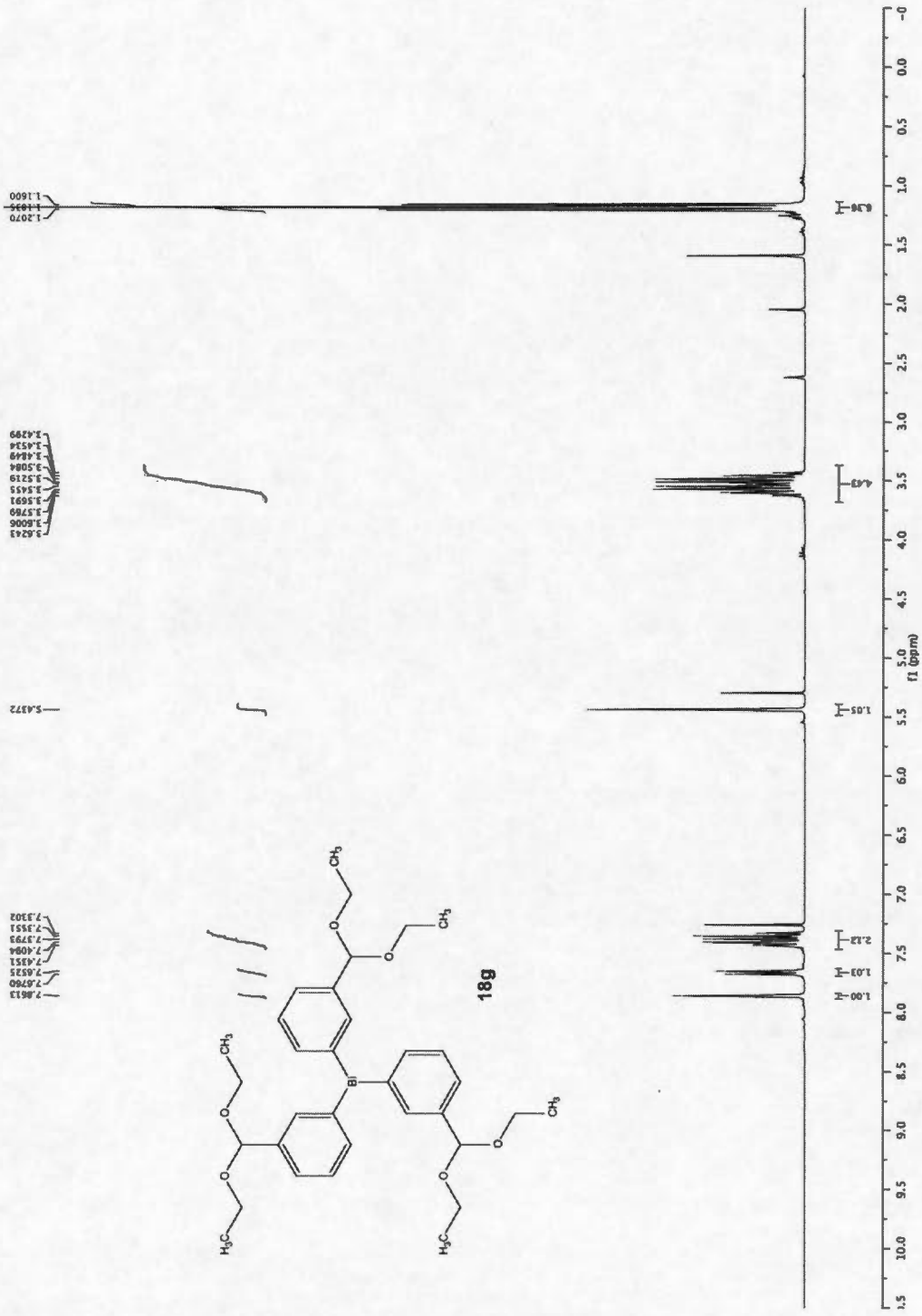
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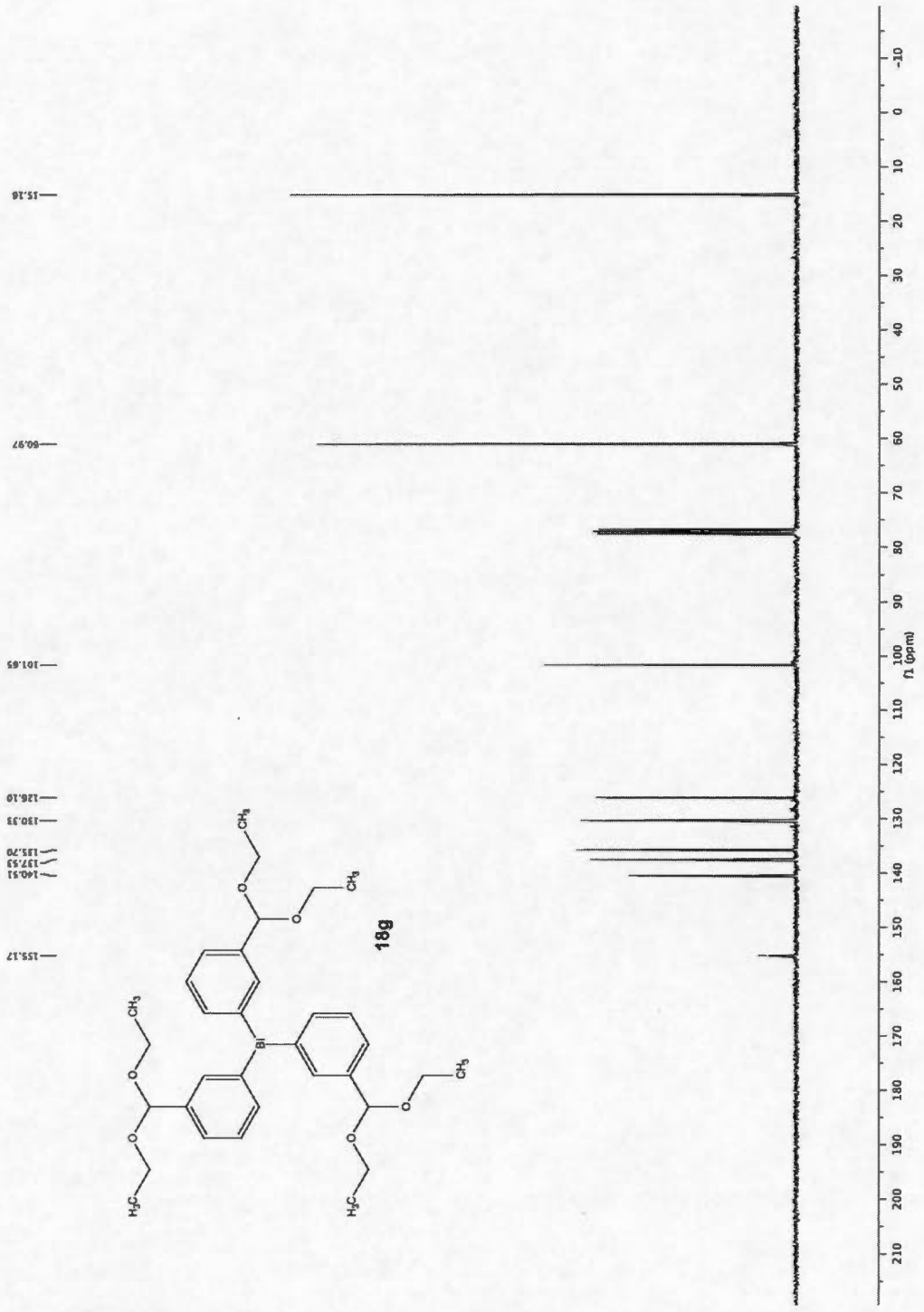
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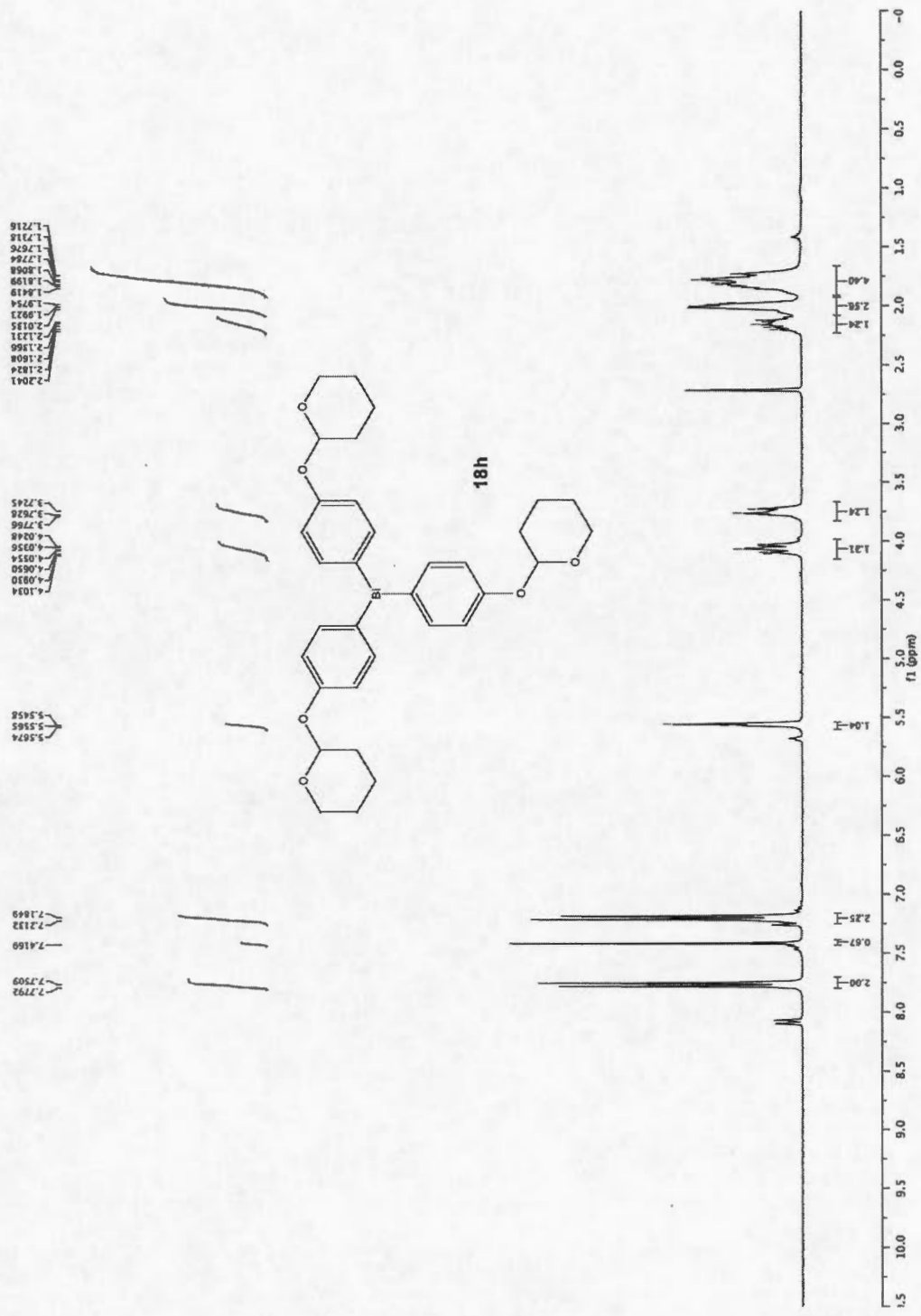
f1 (ppm)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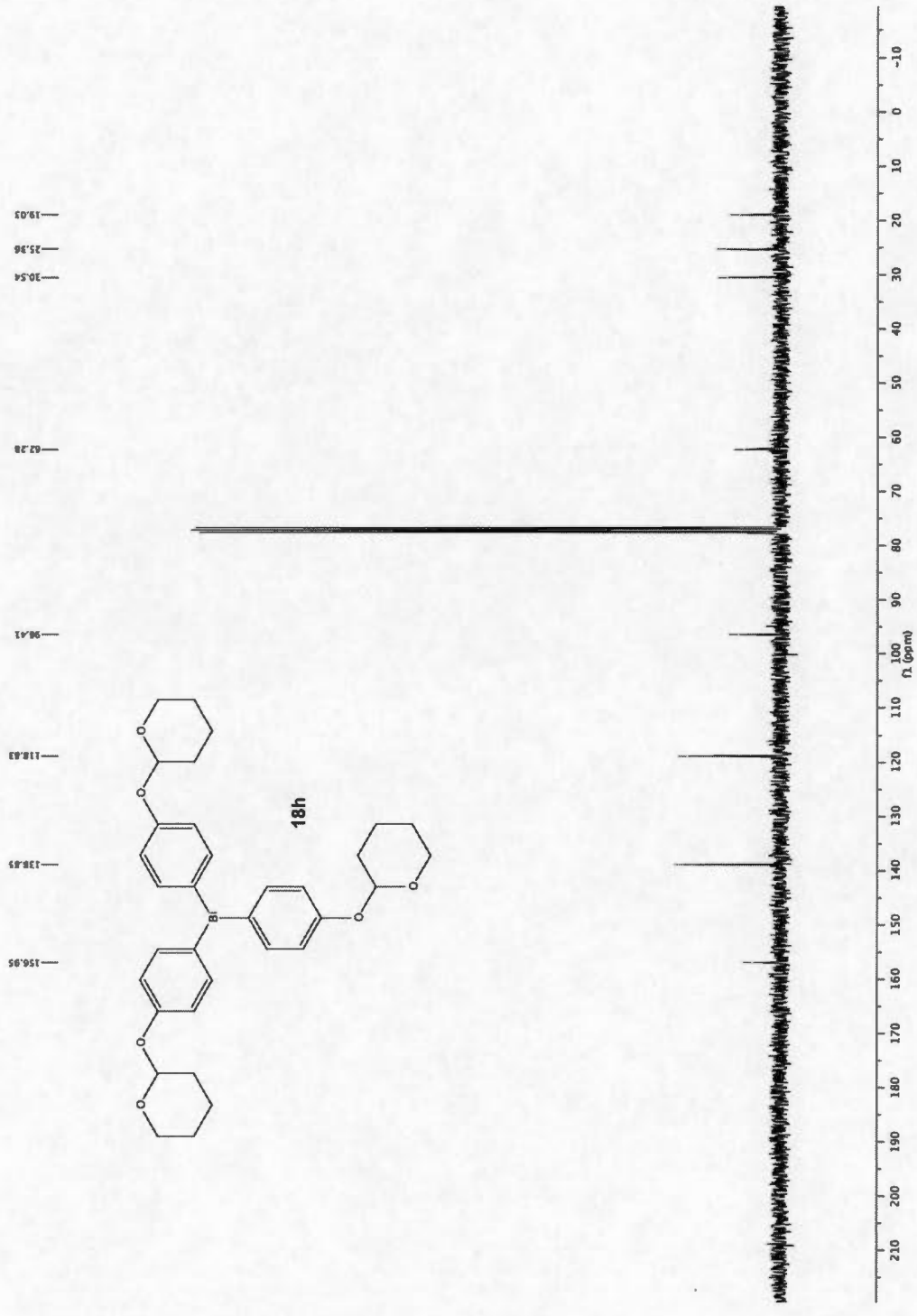
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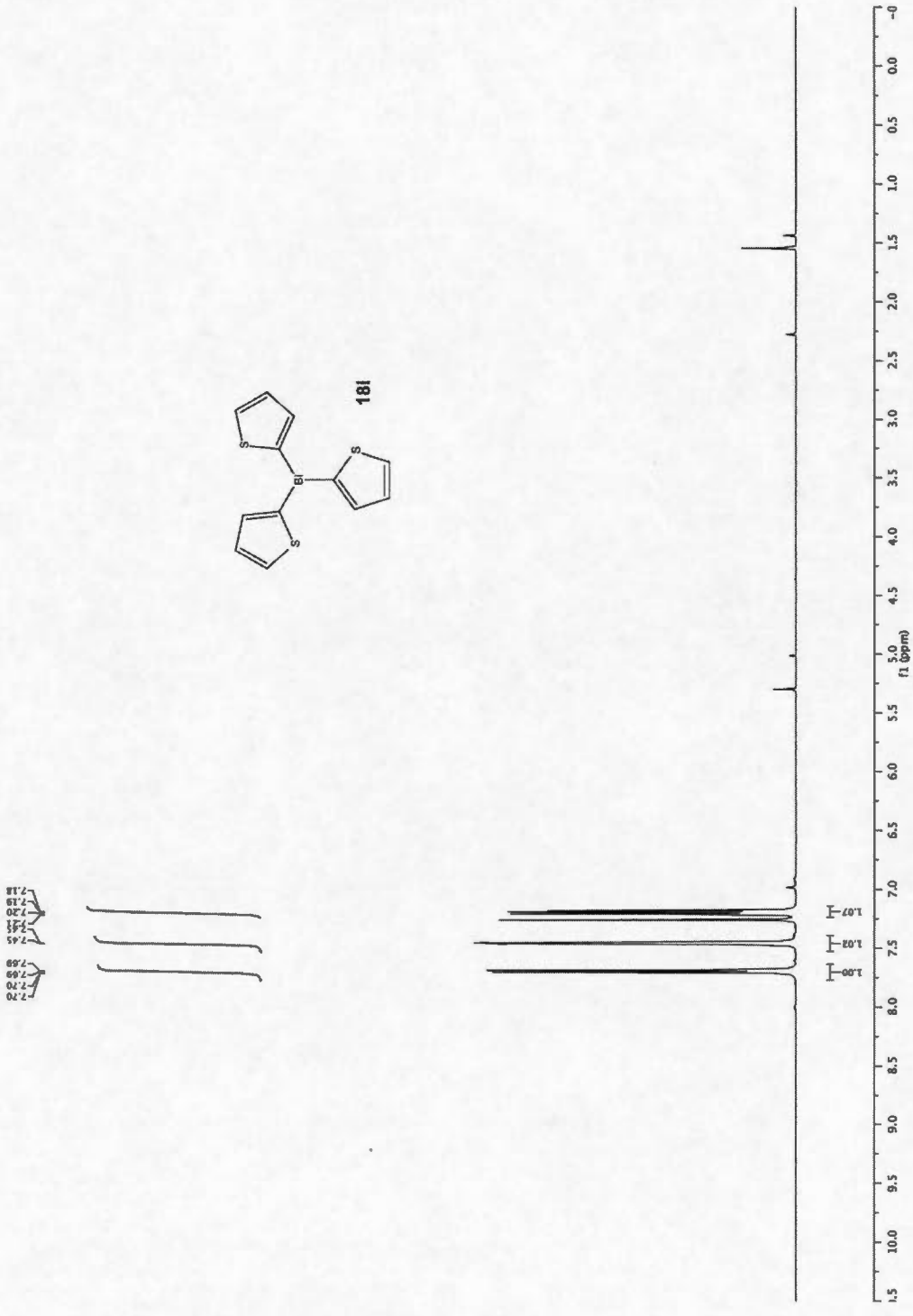
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Bi
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S
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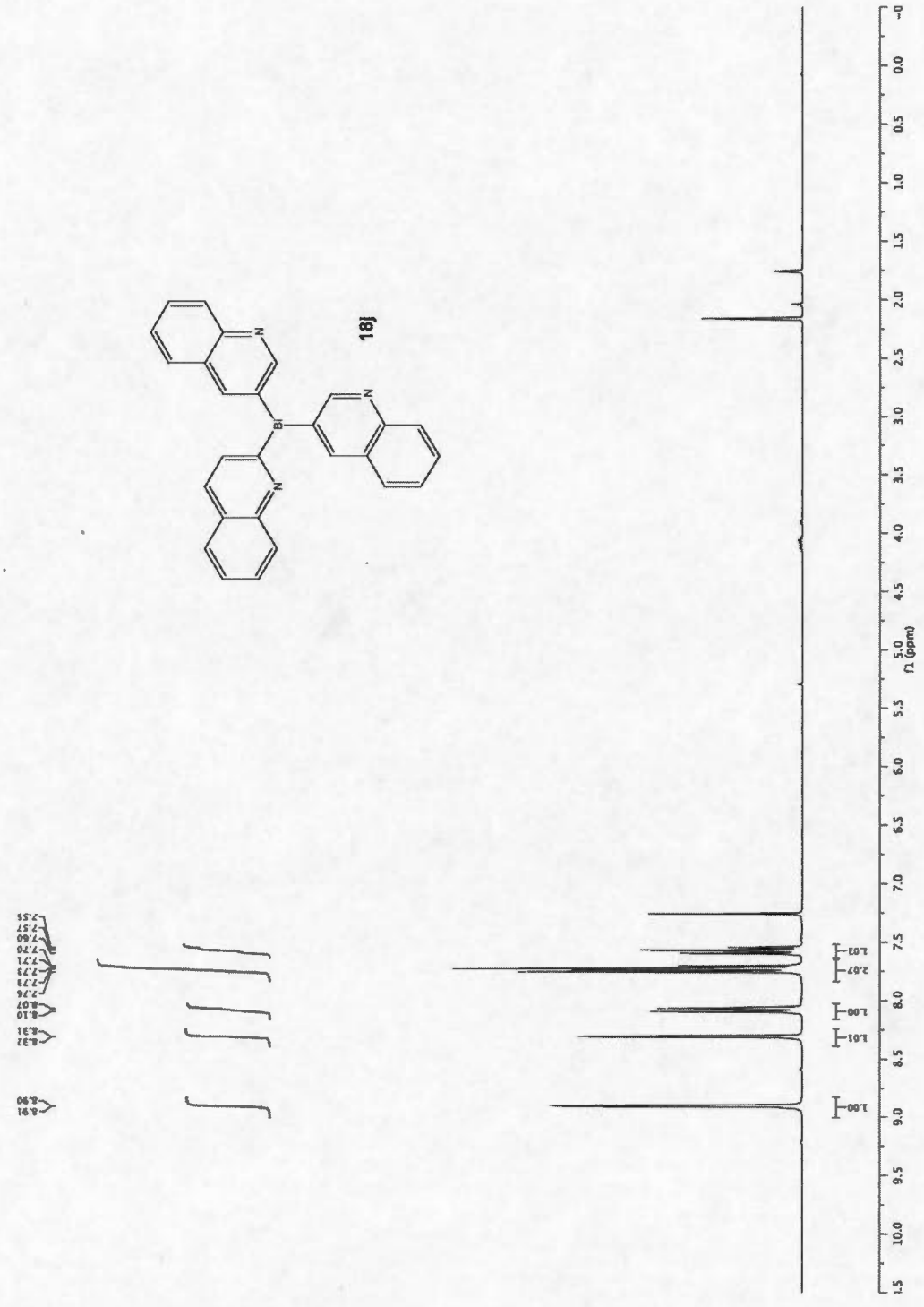
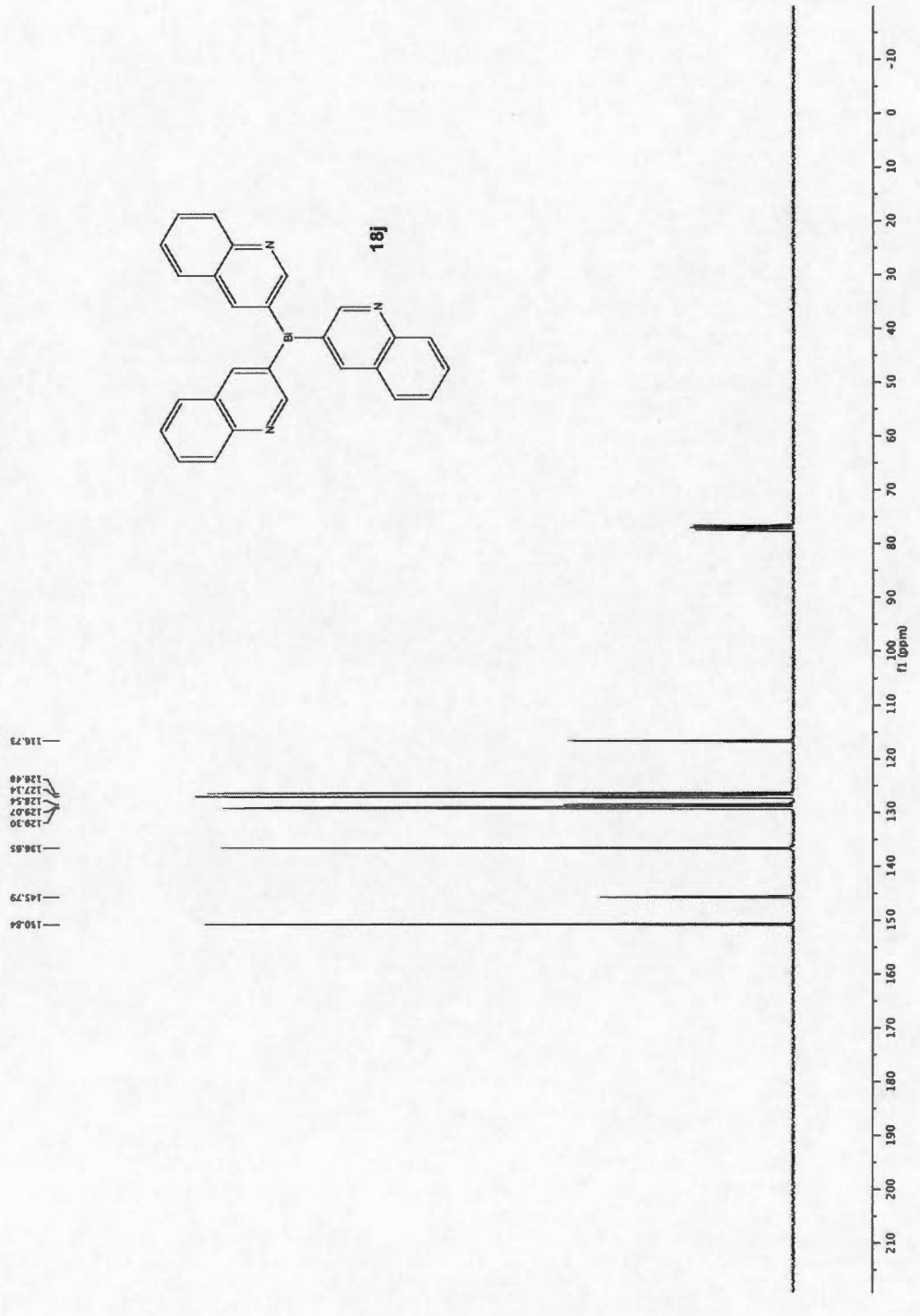
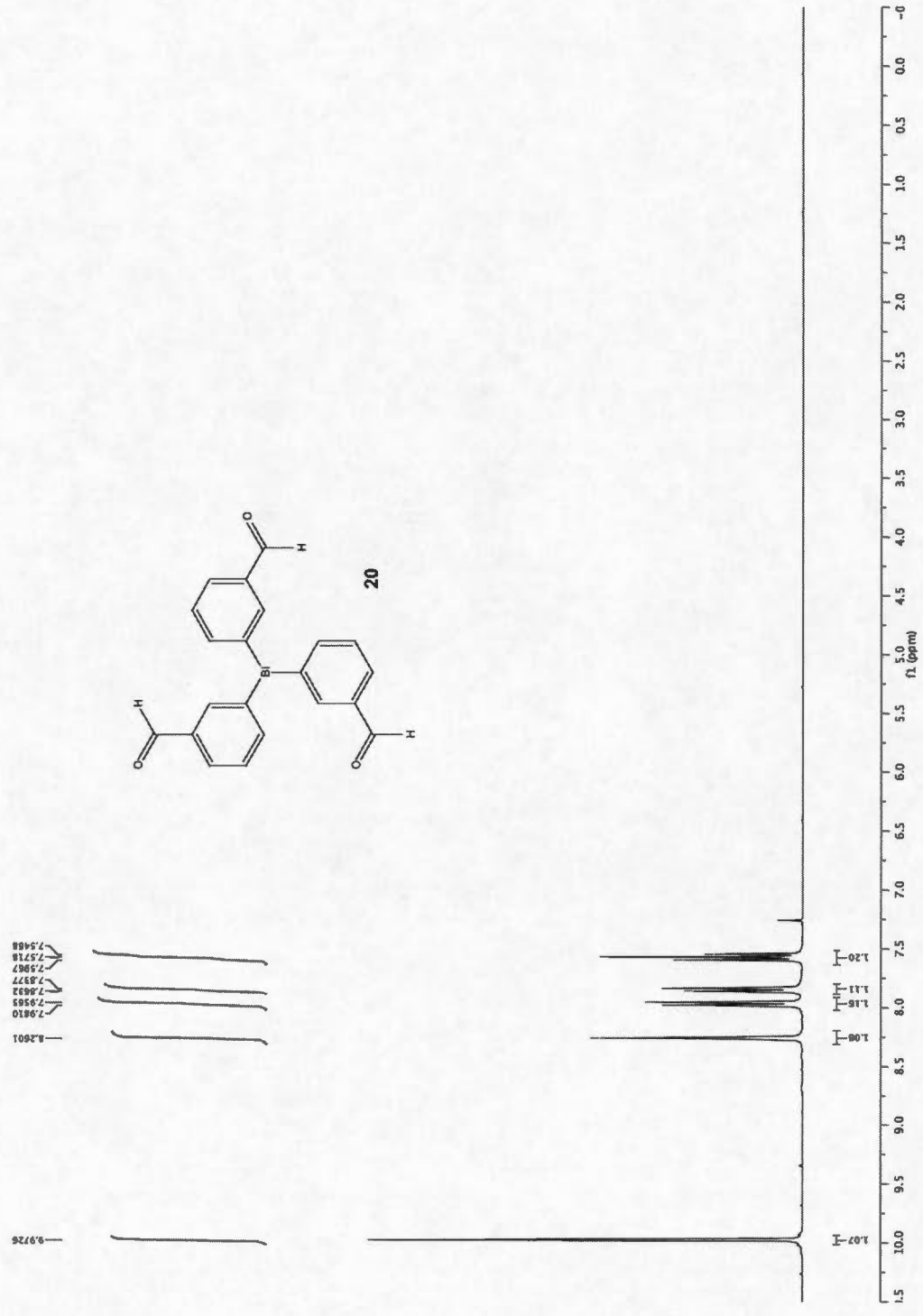
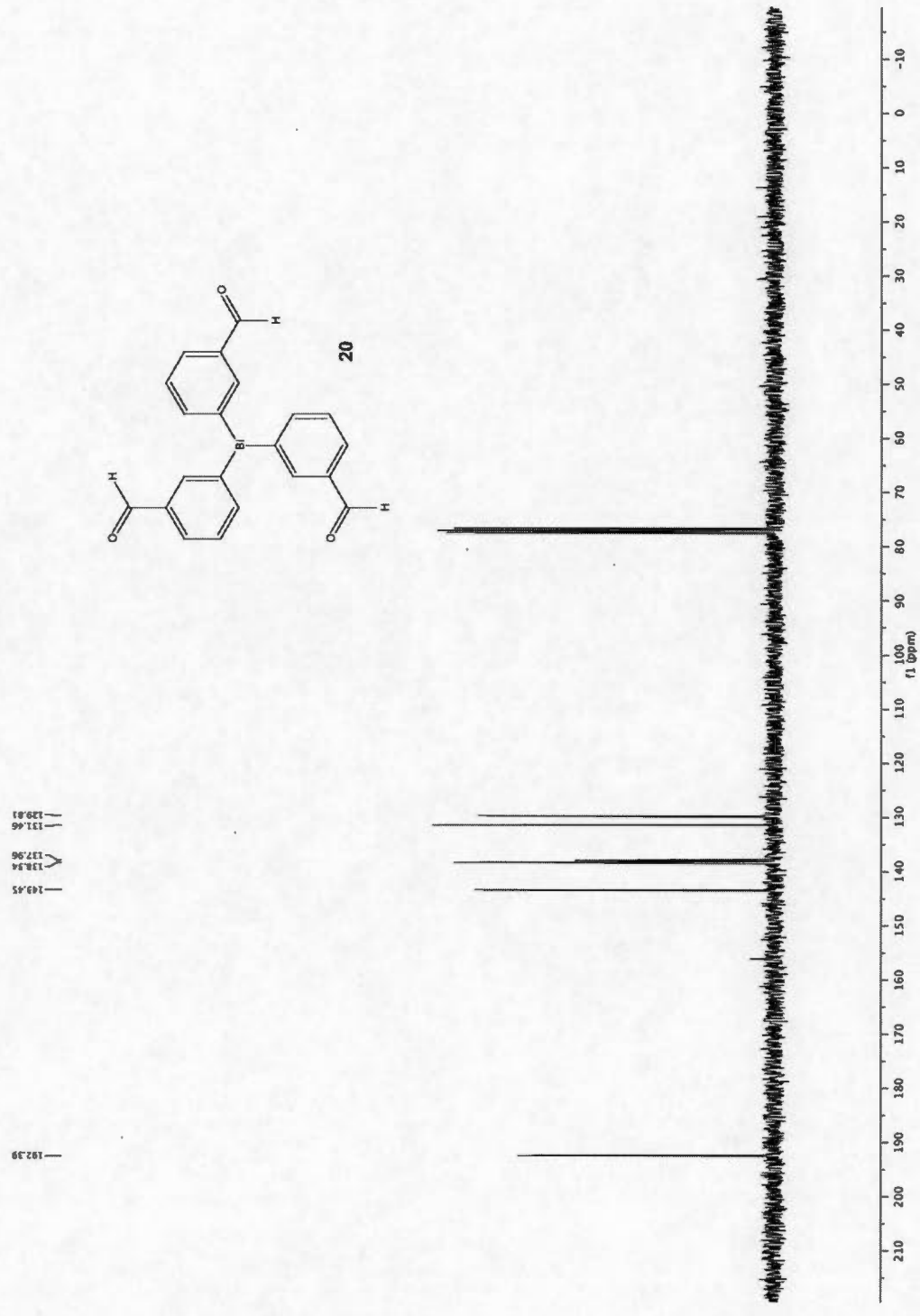
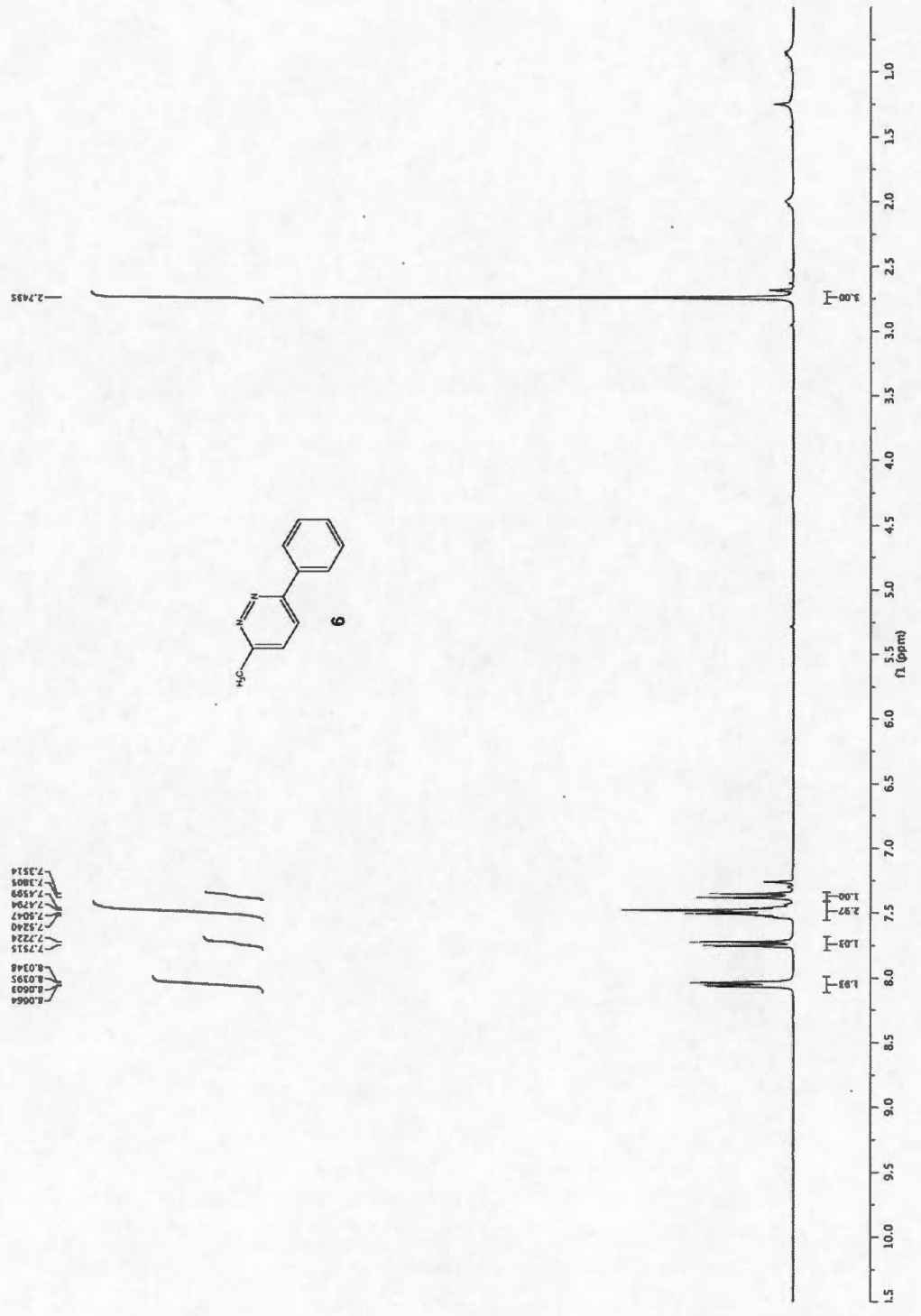
1.02
1.07
5.0
f1 (ppm)

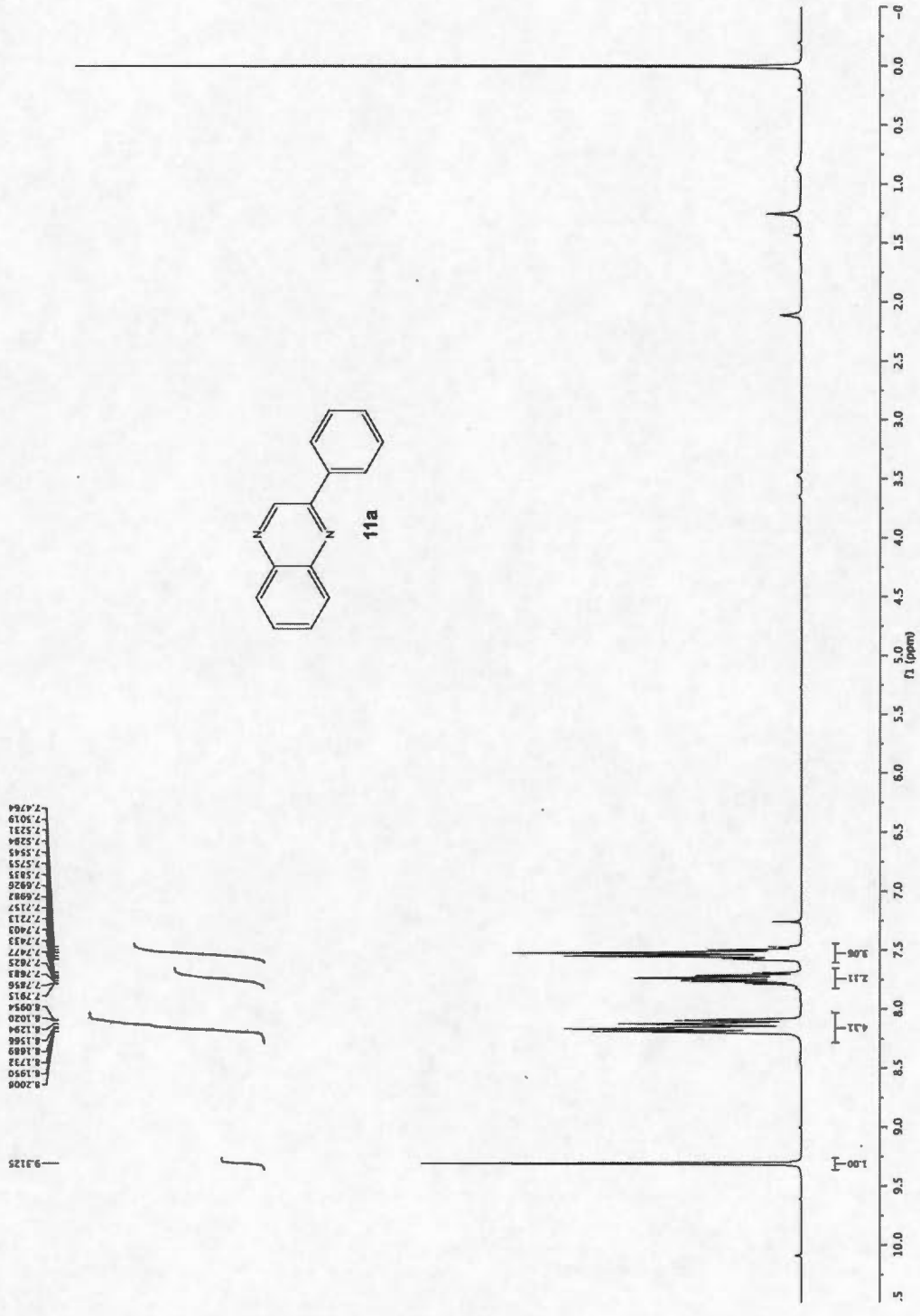

18j
f1 (ppm)

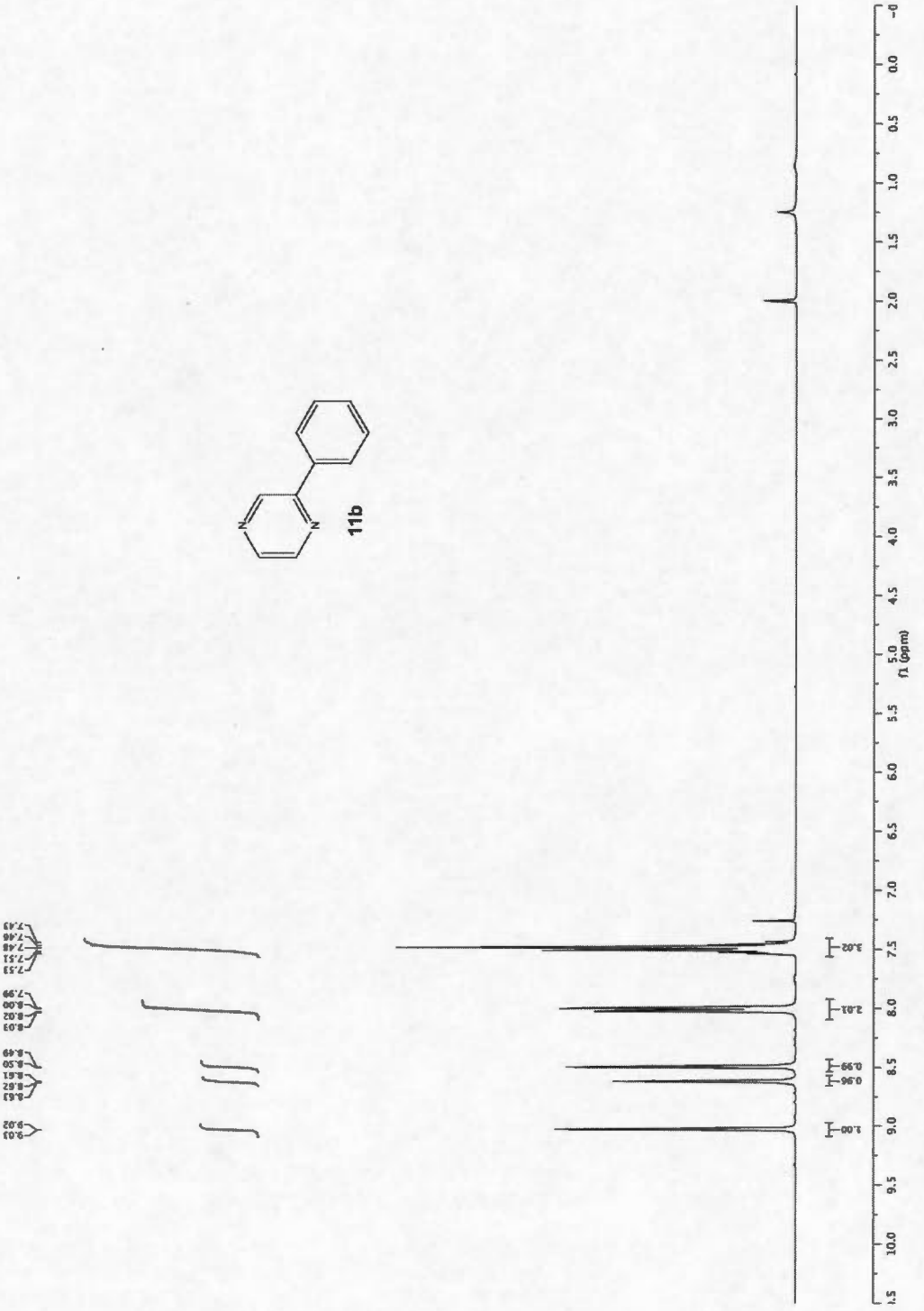

18j
N
N
Bi
N
150.84
145.79
136.85
129.30
129.07
128.54
127.14
126.48
116.73
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
f1 (ppm)

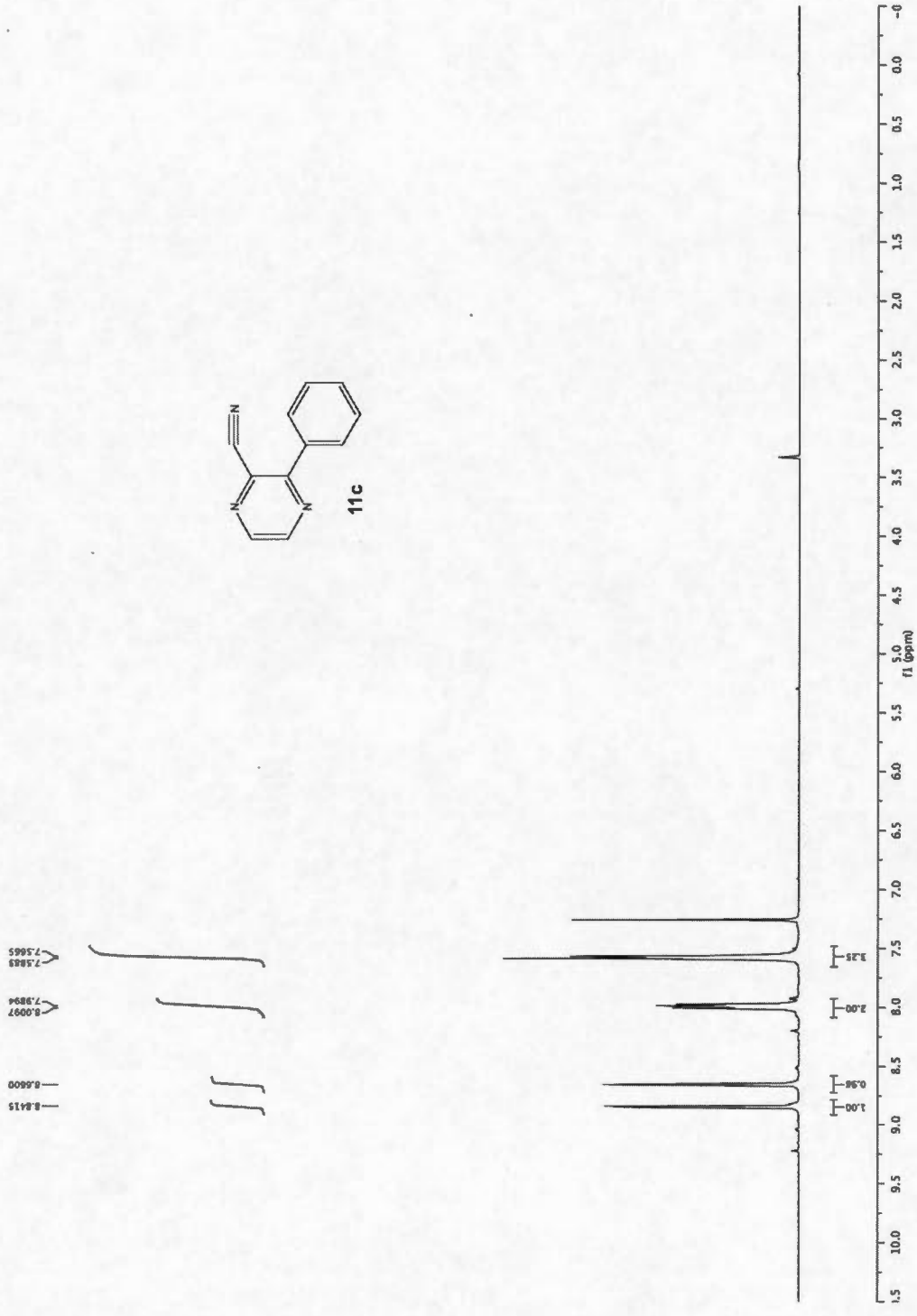

20
9.9726
8.2601
7.9810
7.9565
7.8632
7.8327
7.5967
7.5718
7.5468
1.07
1.08
1.16
1.11
1.20
f1 (ppm)

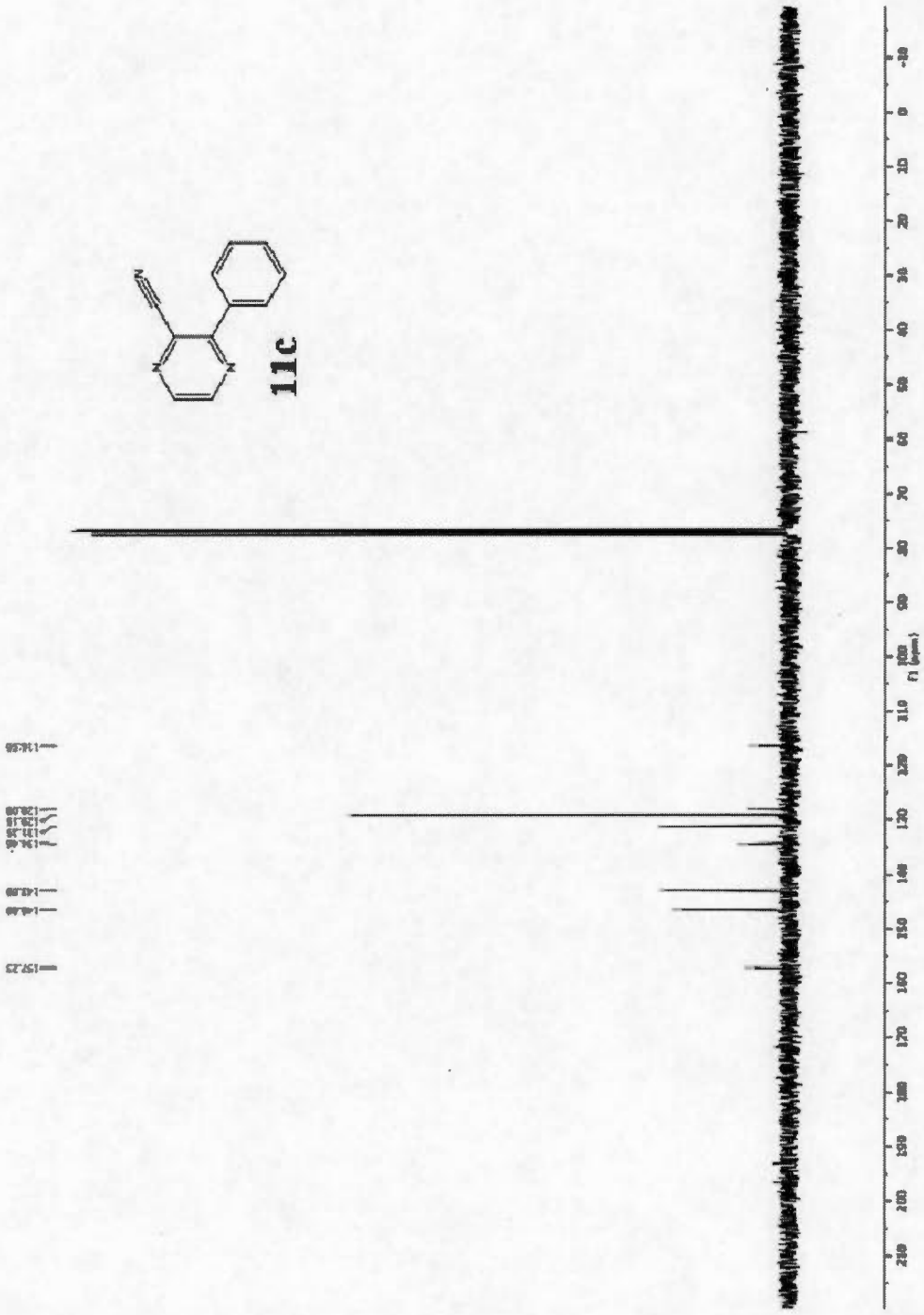

20
192.39
149.45
138.34
137.96
131.46
129.83
f1 (ppm)


8.0064
8.0603
8.0395
8.0348
7.7515
7.7224
7.5240
7.5047
7.4794
7.4589
7.3805
7.3514
2.7495
3.00
1.93
1.03
2.97
1.00
f1 (ppm)
6

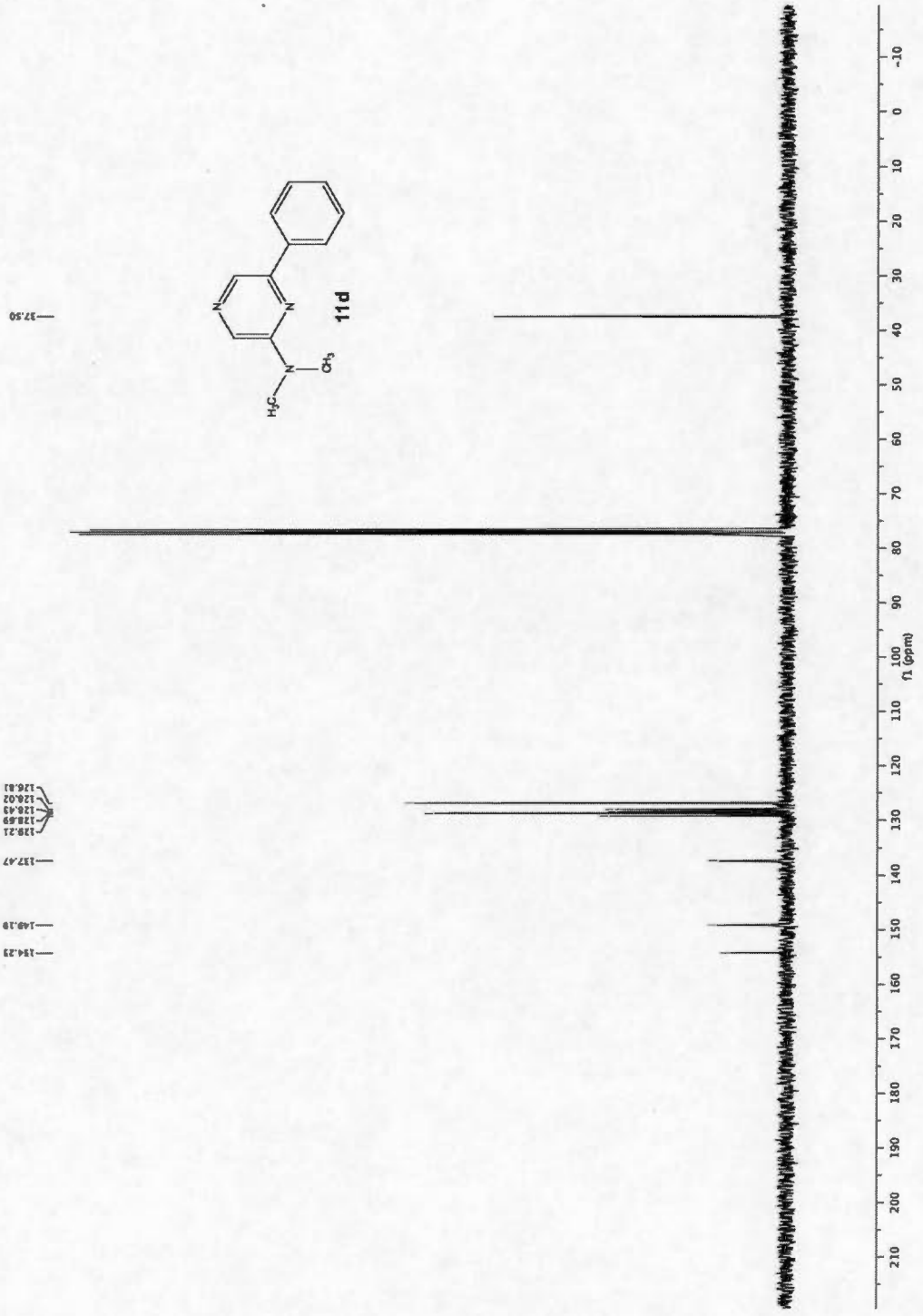

11a
f1 (ppm)
1.00
4.32
2.11
3.06
9.3125
8.2008
8.1950
8.1732
8.1689
8.1566
8.1294
8.1020
8.0954
7.7915
7.7856
7.7683
7.7625
7.7477
7.7433
7.7403
7.7213
7.7157
7.6982
7.6926
7.5835
7.5755
7.5545
7.5294
7.5231
7.3019
7.4764

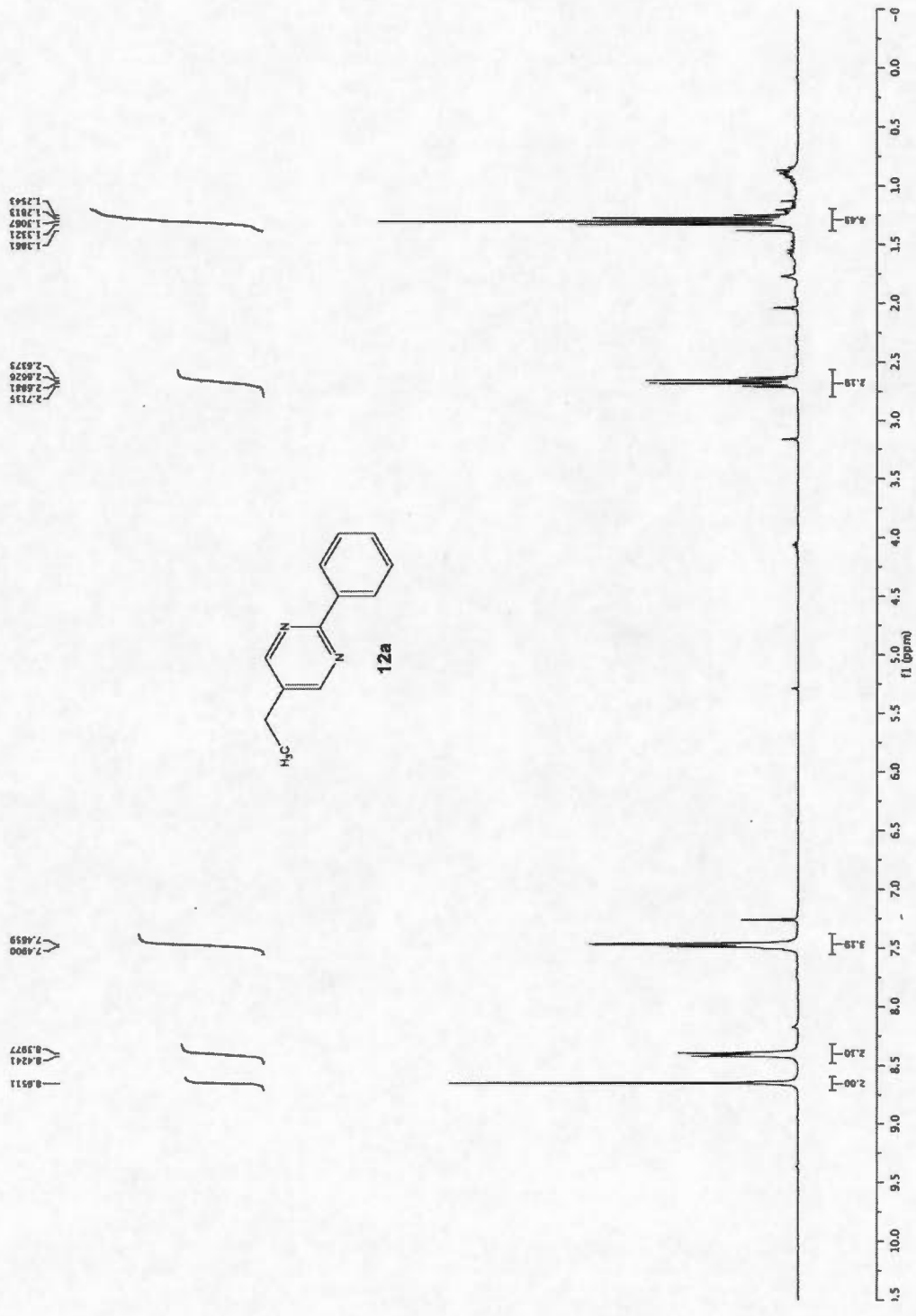

11b
9.02
8.63
8.62
8.51
8.50
8.49
8.03
8.02
7.99
7.53
7.51
7.48
7.46
7.43
3.02
2.01
0.96
0.99
1.00
f1 (ppm)

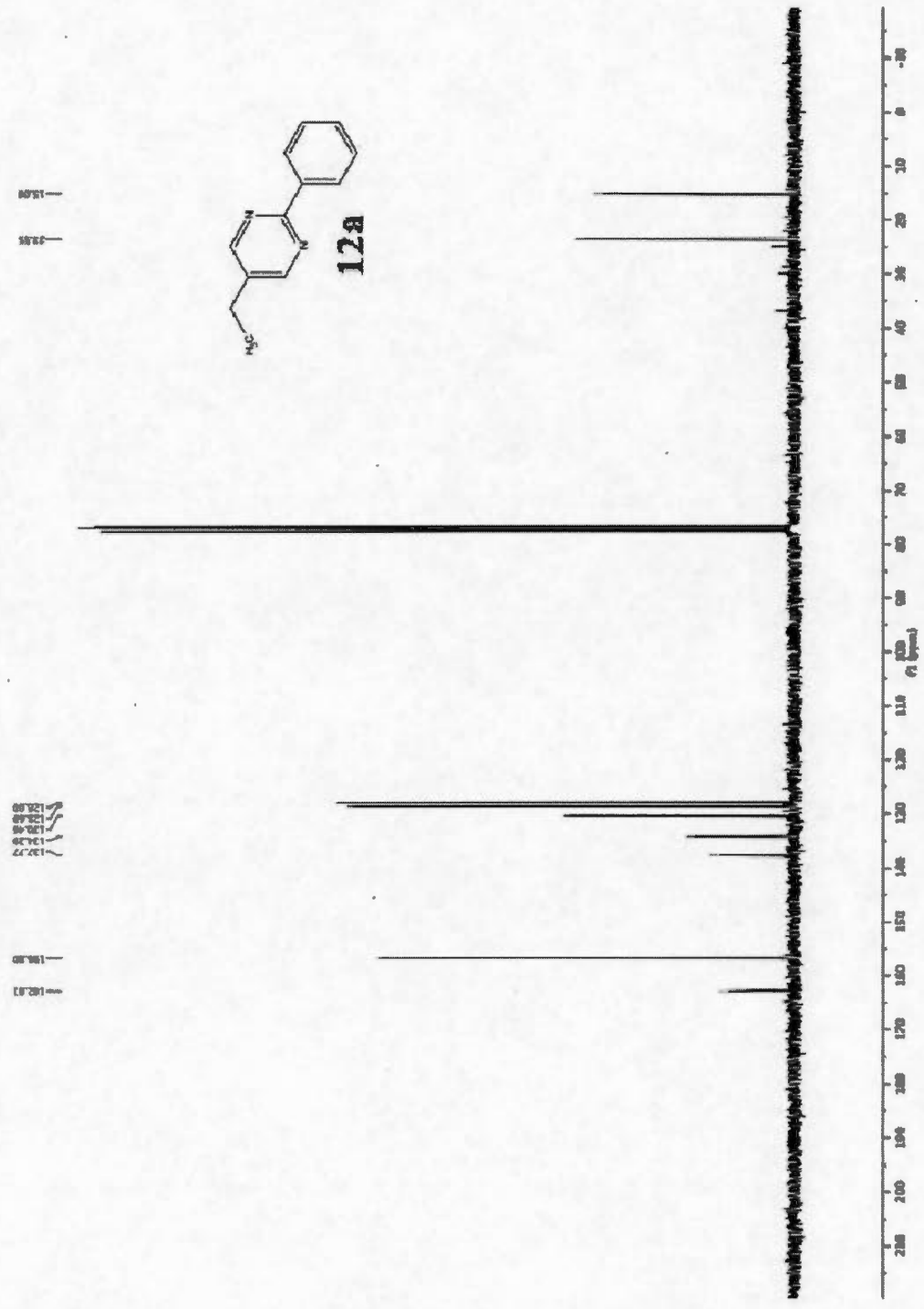

11c
8.8415
8.6600
8.0097
7.9894
7.5885
7.5665
1.00
0.96
2.00
3.35
f1 (ppm)

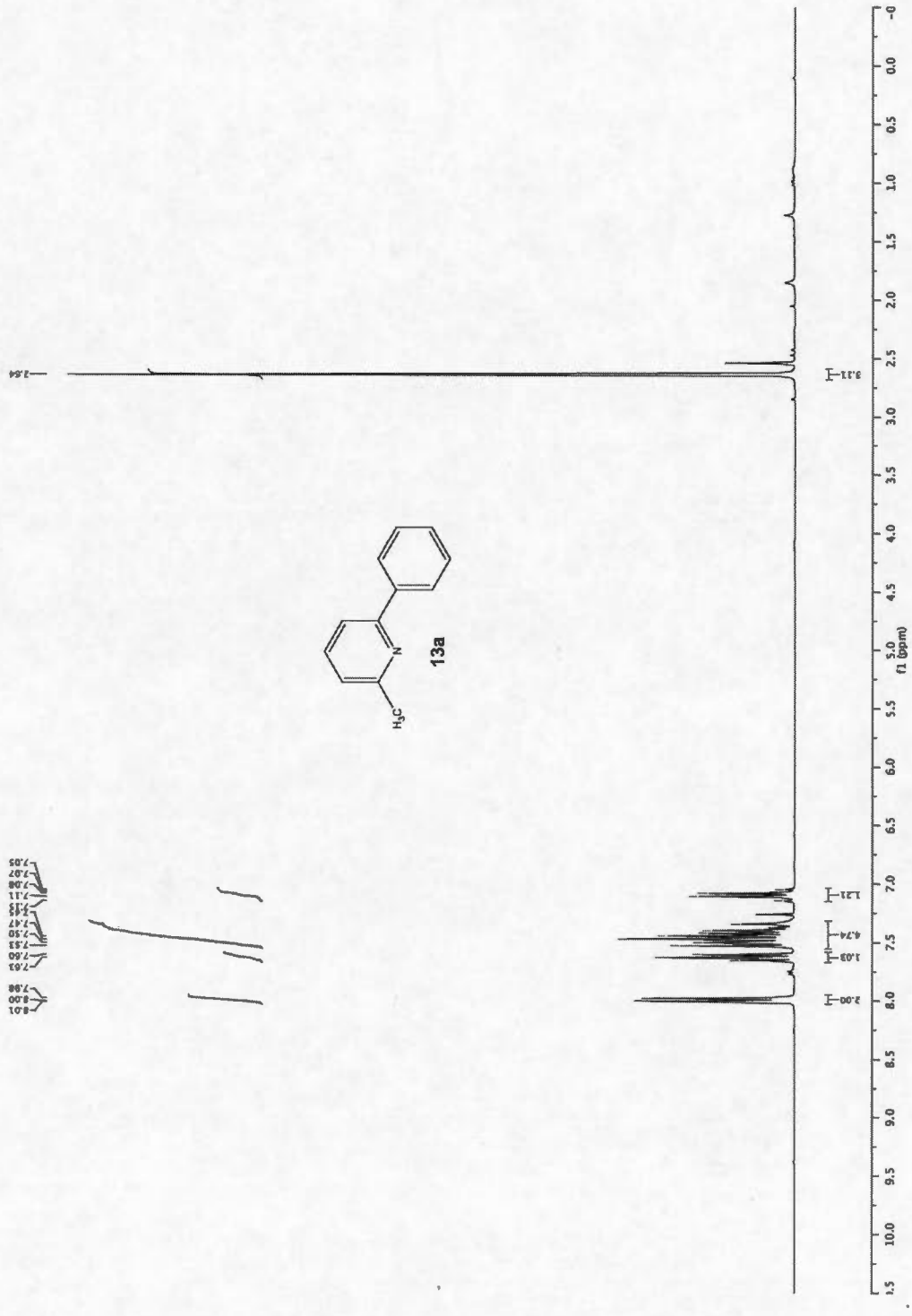

11c

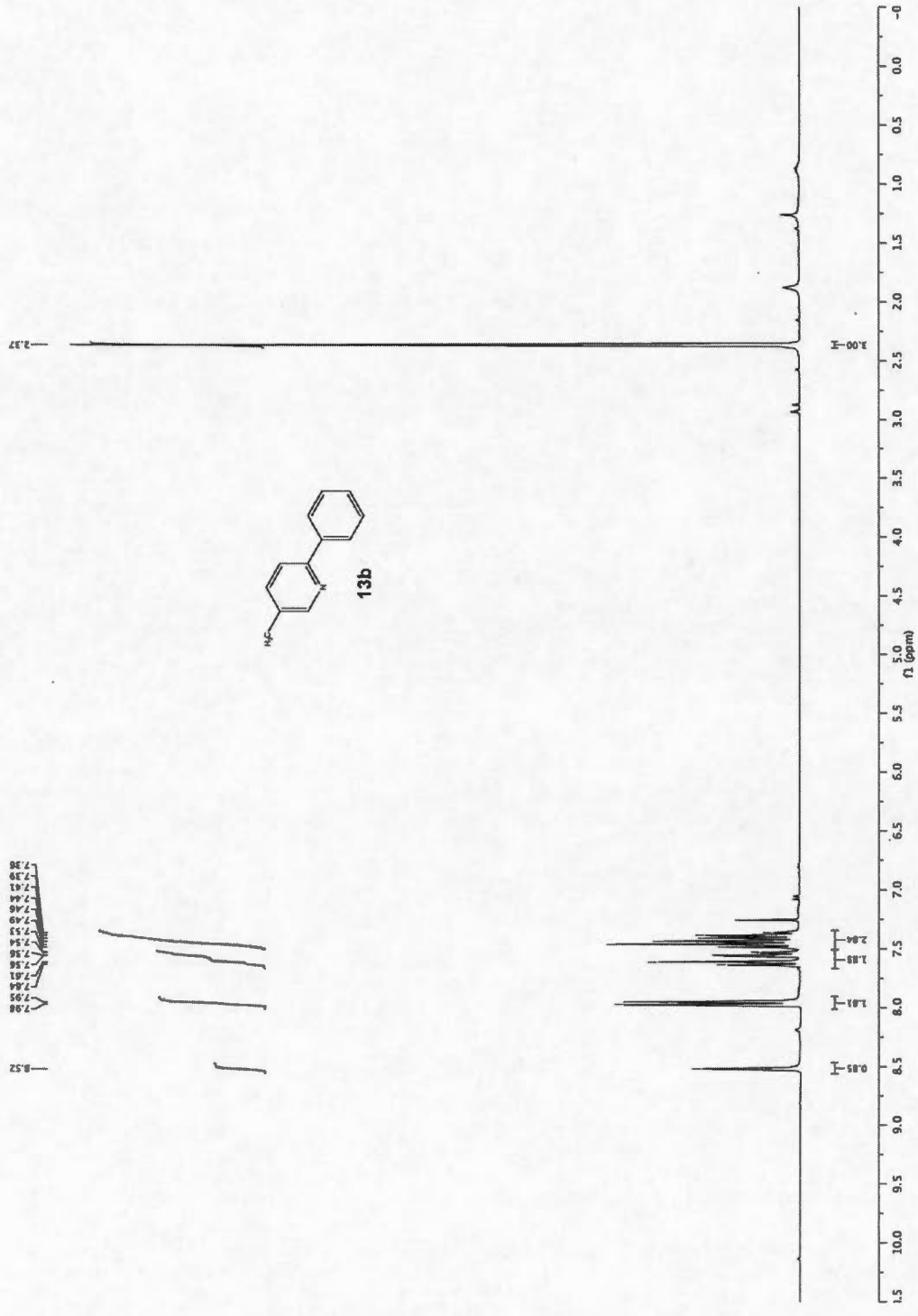

11d
f1 (ppm)


11d
37,50
134,23
140,19
137,47
128,21
128,89
128,49
126,02
126,81
f1 (ppm)

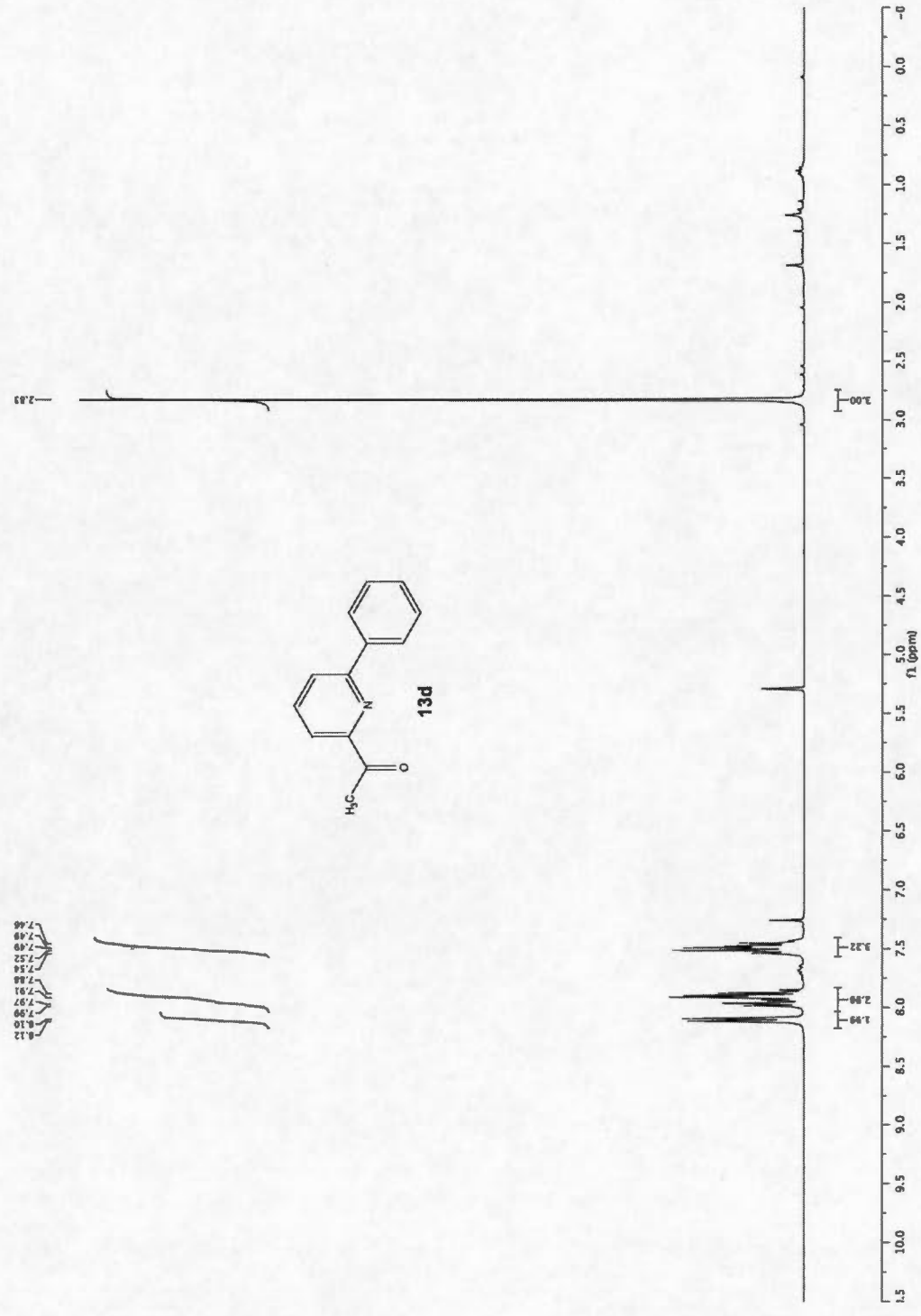

8.9511
8.4241
8.3977
7.4900
7.4659
2.7135
2.6841
2.6626
2.6373
1.3061
1.3321
1.3067
1.2813
1.2563
2.00
2.10
3.18
2.18
4.49
f1 (ppm)
12a

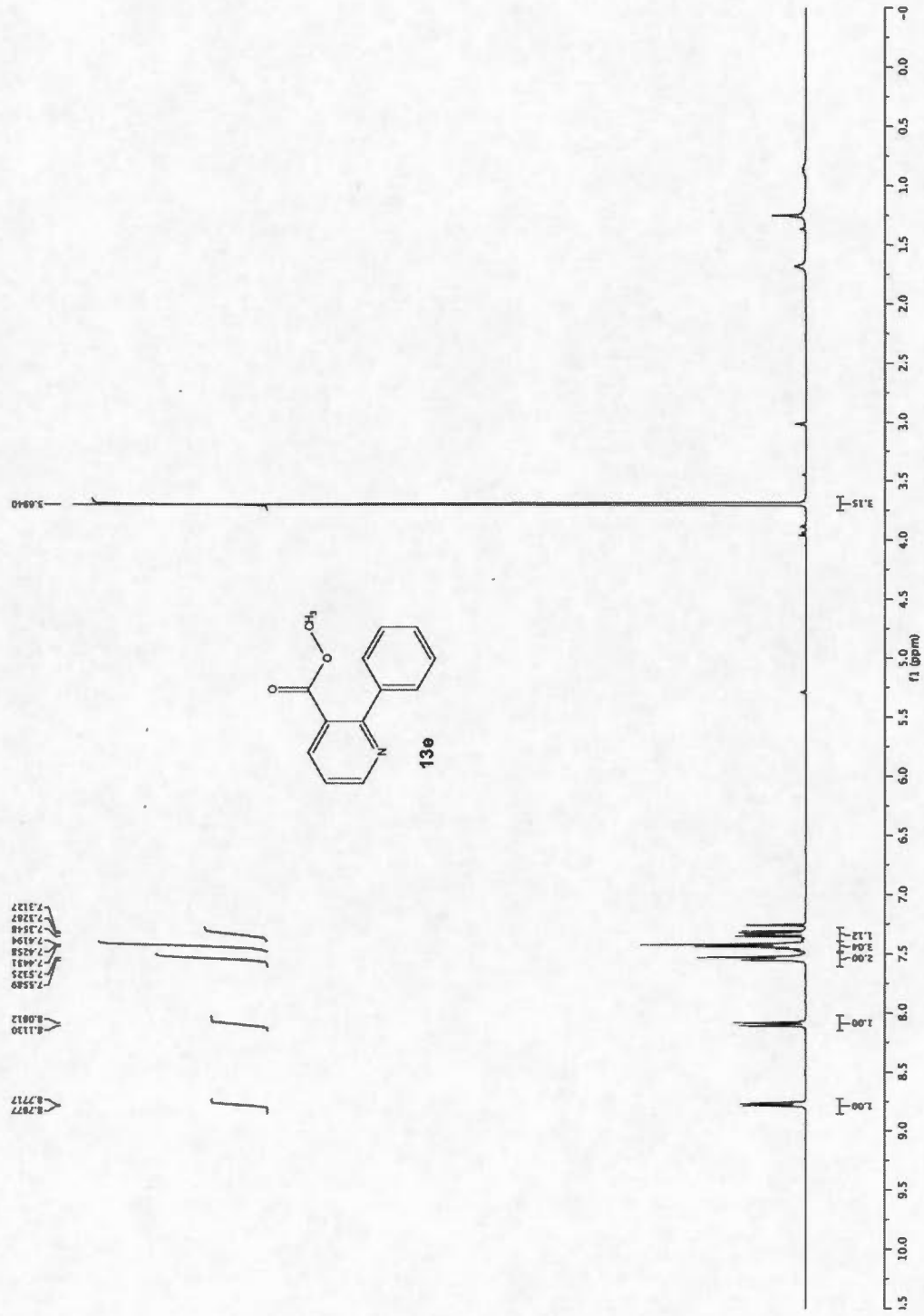

12a

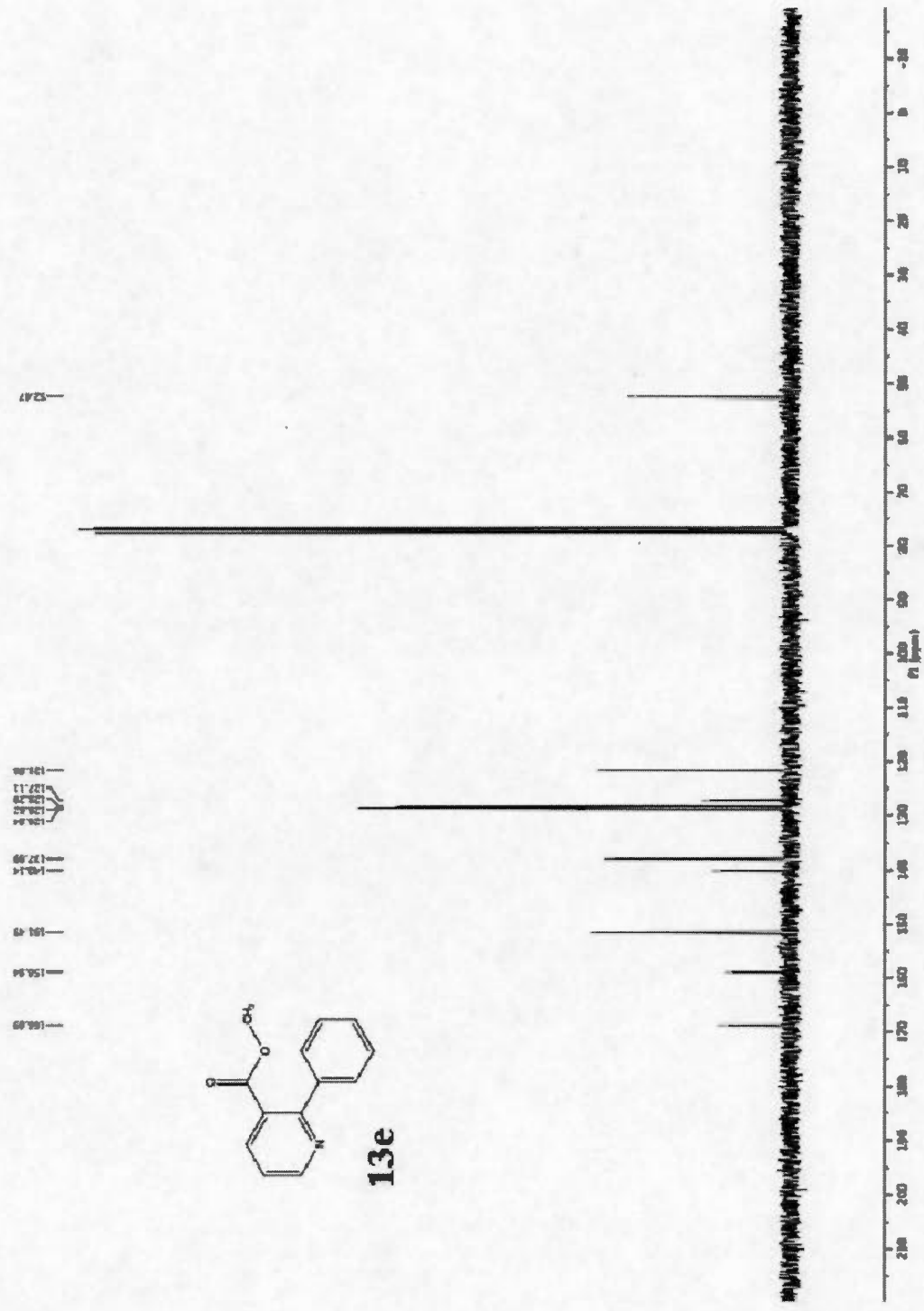

13a
N
H3C
2.54
8.01
8.00
7.98
7.63
7.60
7.53
7.50
7.47
7.35
7.33
7.11
7.08
7.07
7.05
3.11
2.00
1.03
4.74
1.21
f1 (ppm)


13b
f1 (ppm)

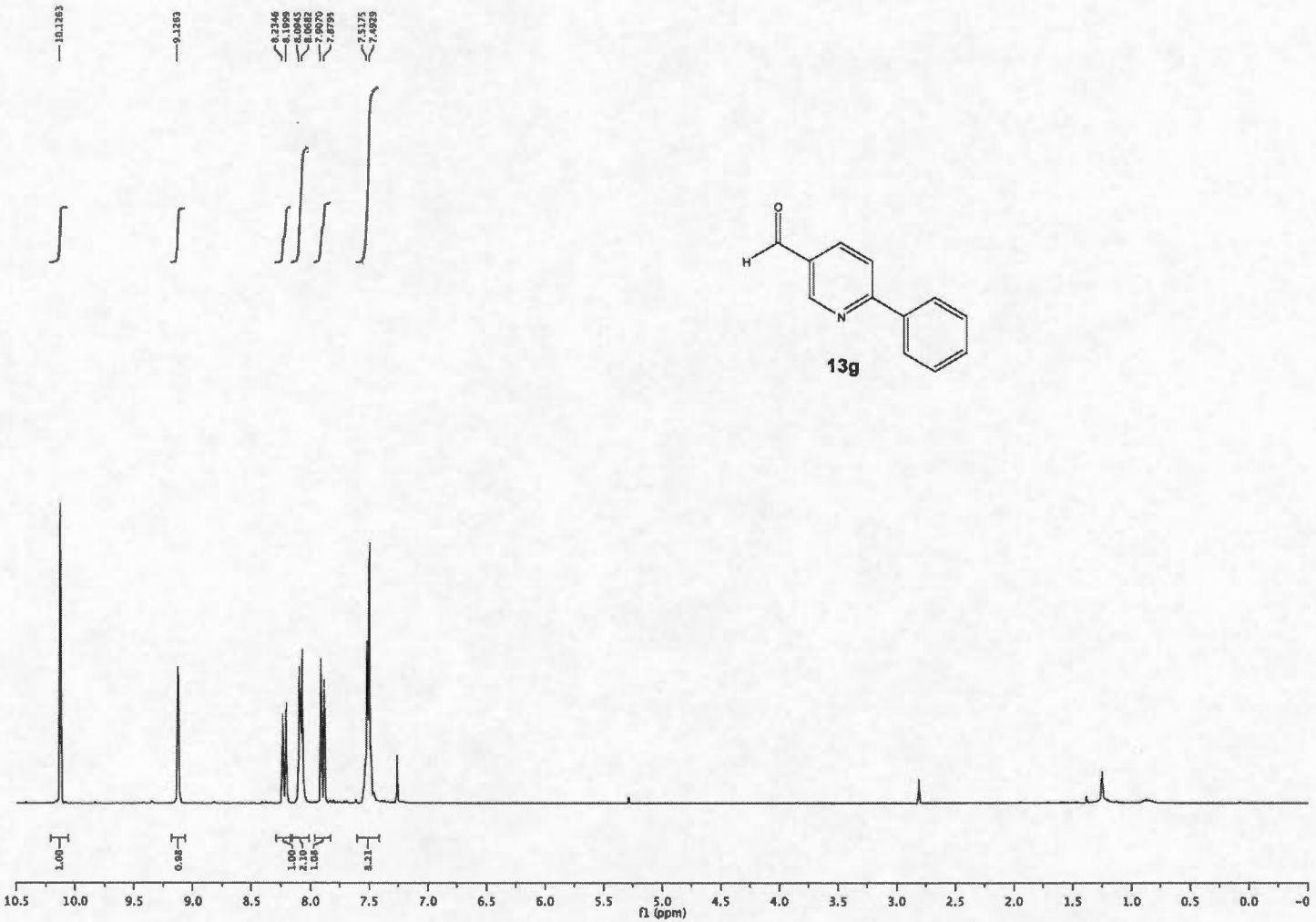
13c
3.00
3.01
3.05
2.03
3.24
f1 (ppm)

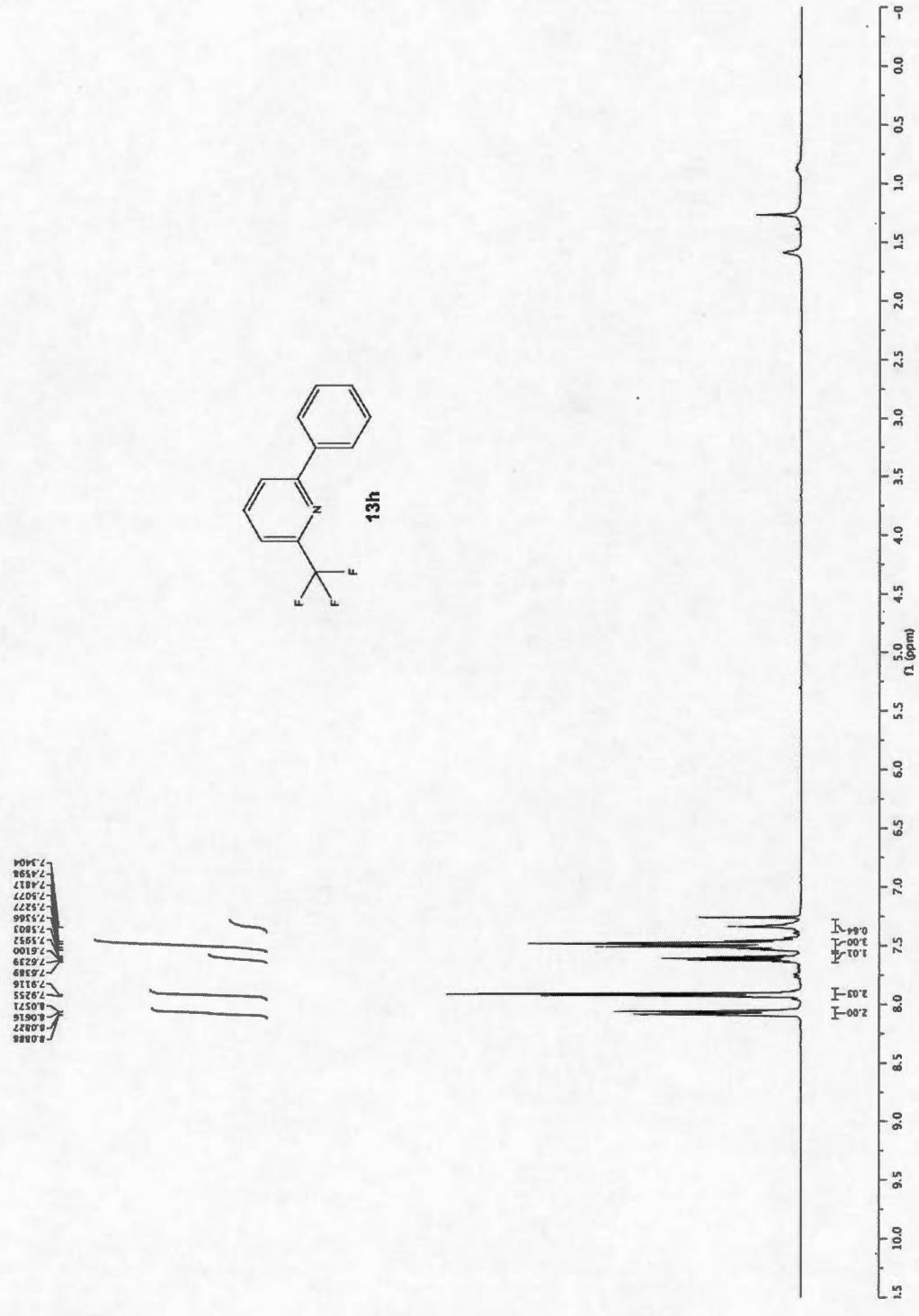

13d
f1 (ppm)

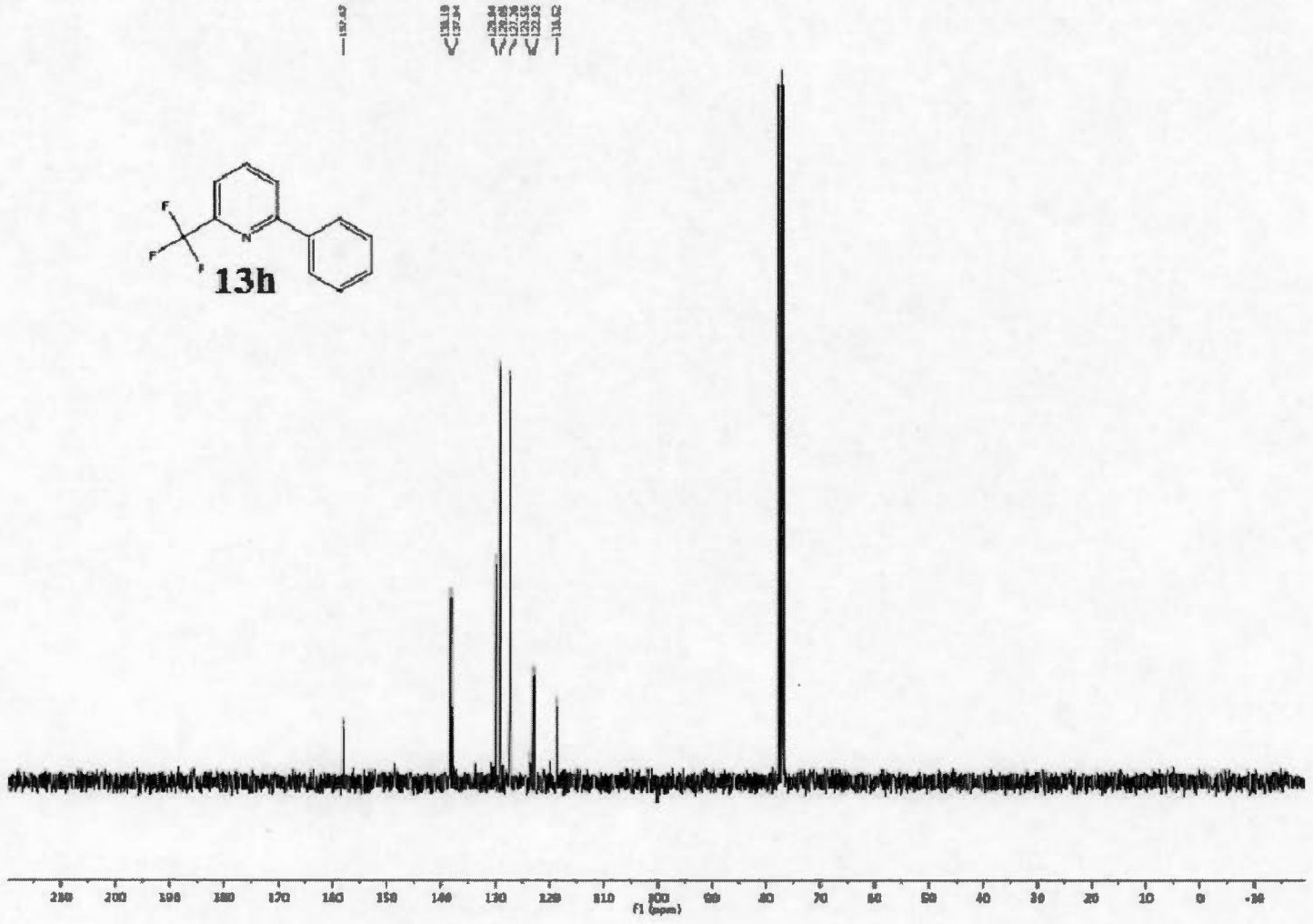

13e
f1 (ppm)

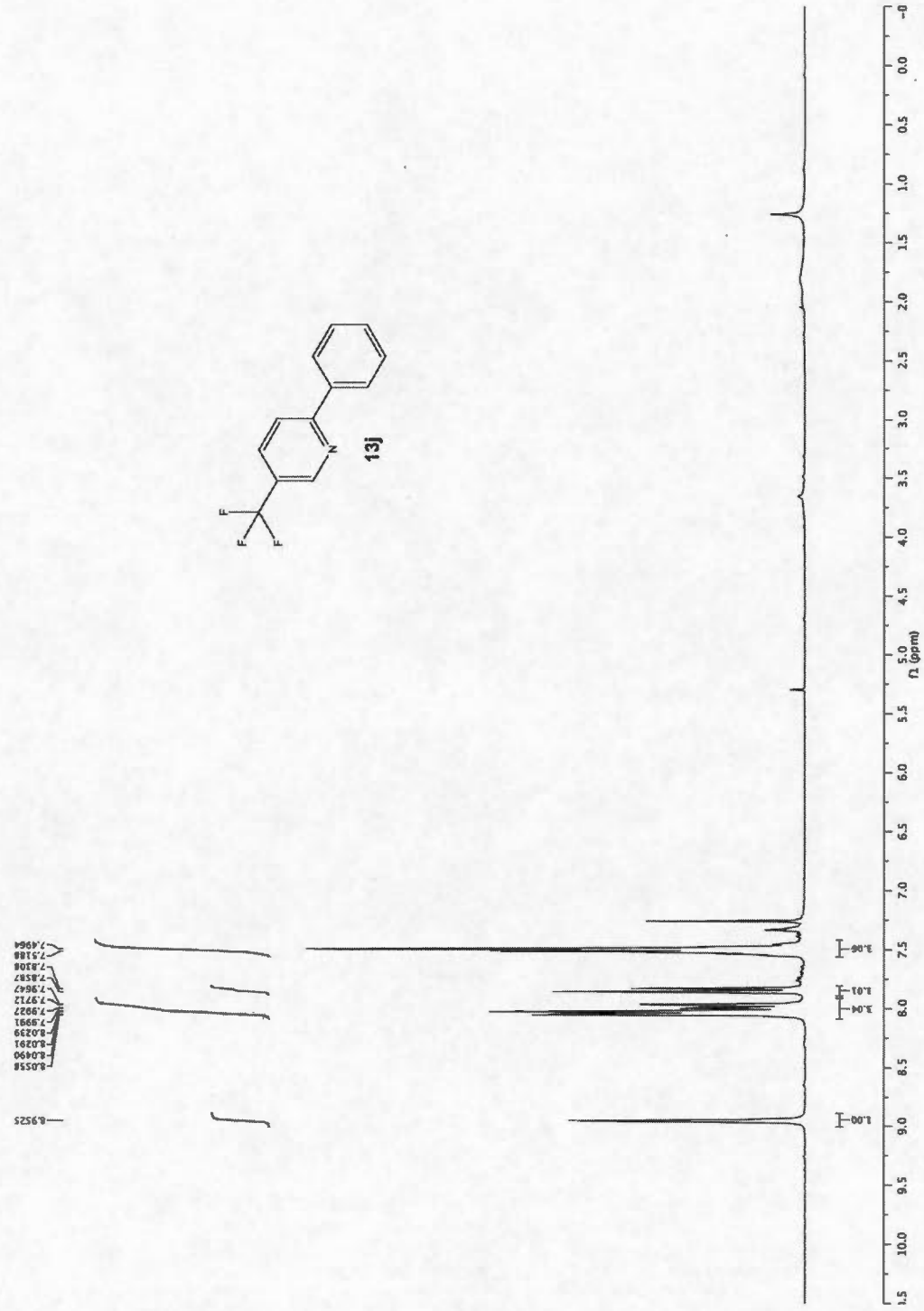


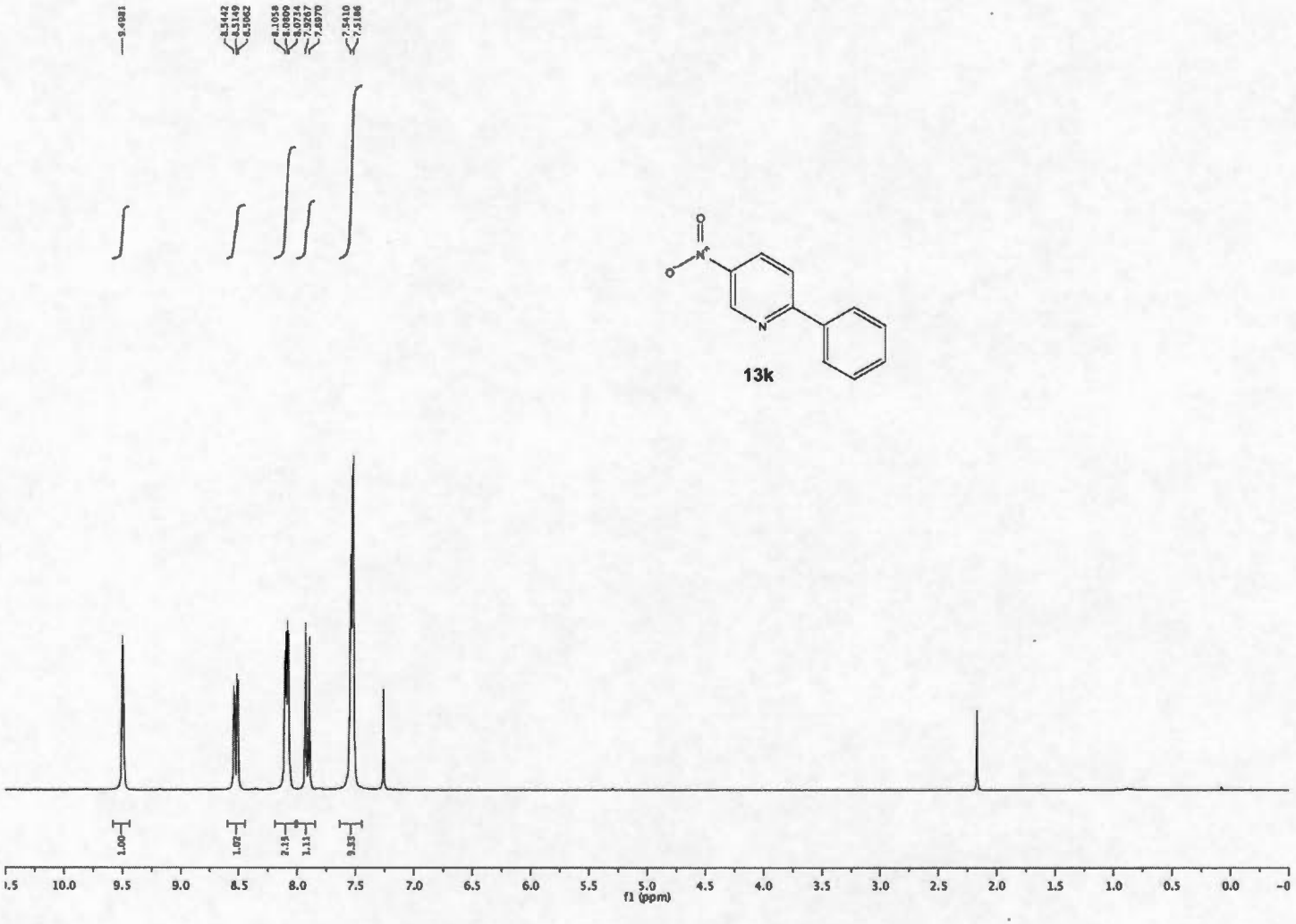
13e

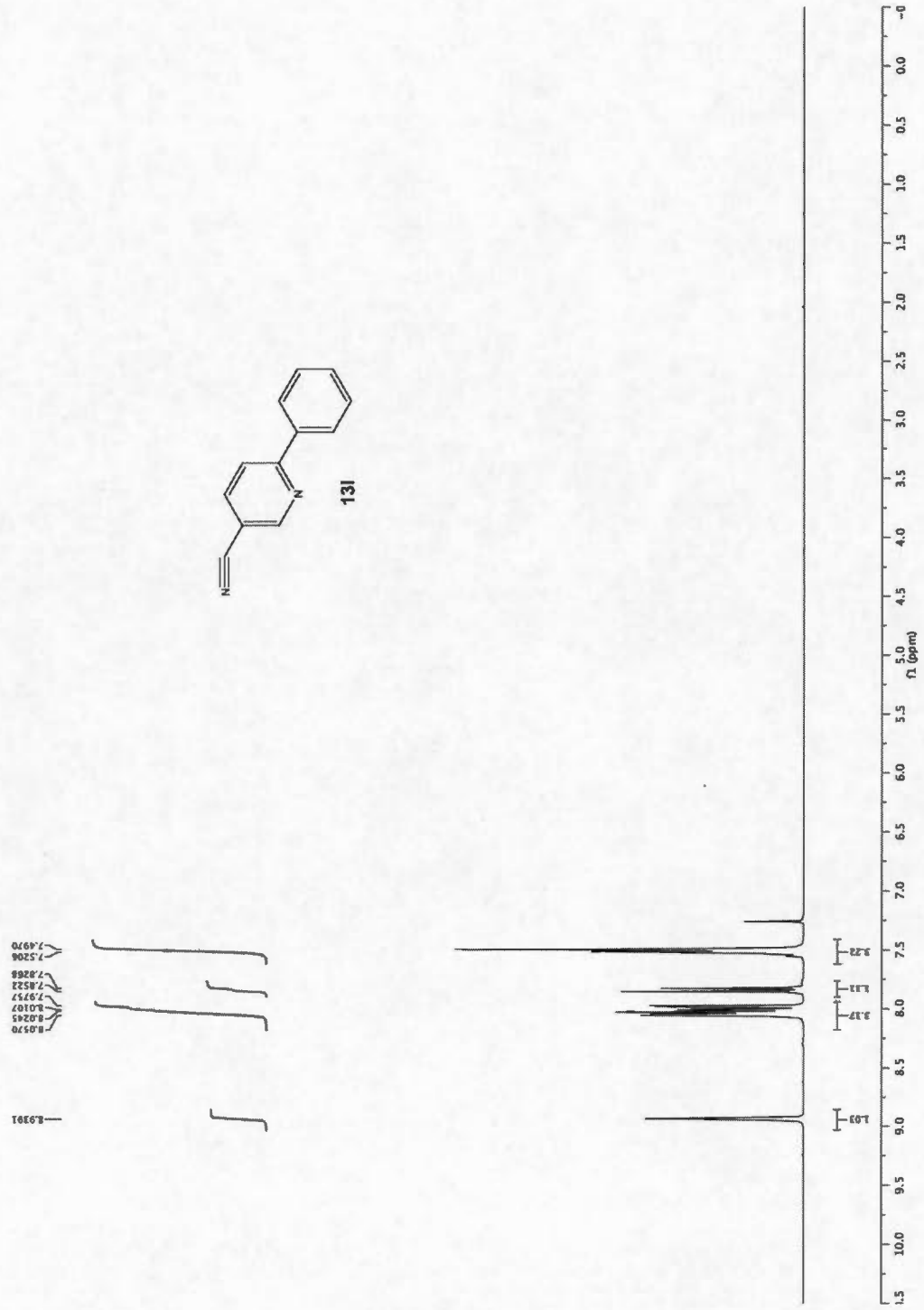

10.1263
9.1263
8.2346
8.1999
8.0945
8.0682
7.9070
7.8799
7.5175
7.4929
O
H
N
13g
1.00
0.88
1.00
2.10
1.05
3.21
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)

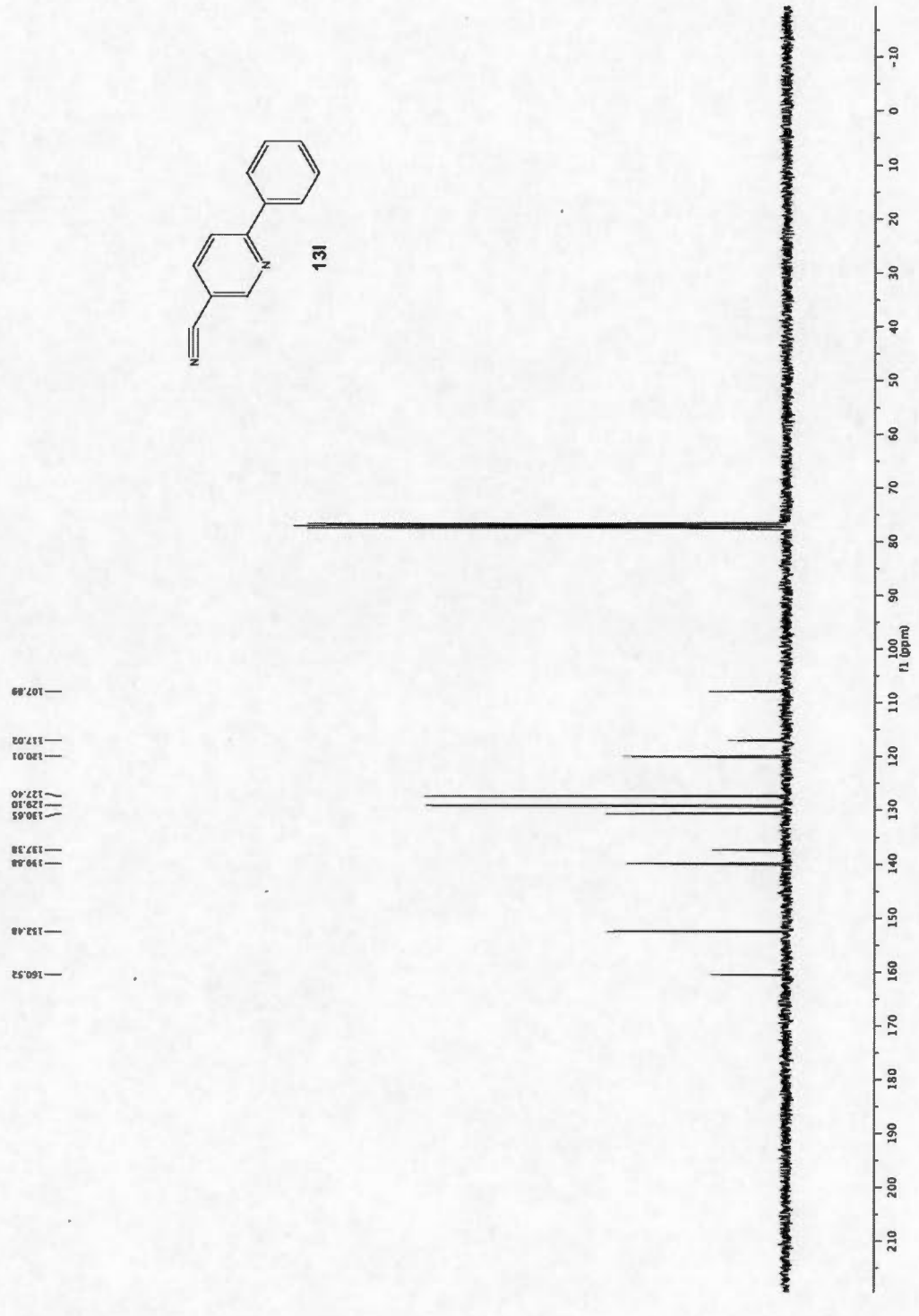

13h
F
F
F
N
8.0888
8.0827
8.0616
8.0571
7.9255
7.9116
7.6389
7.6239
7.6100
7.5952
7.5803
7.5366
7.5277
7.5077
7.4817
7.4598
7.3404
0.84
2.01
3.00
2.03
2.00
f1 (ppm)

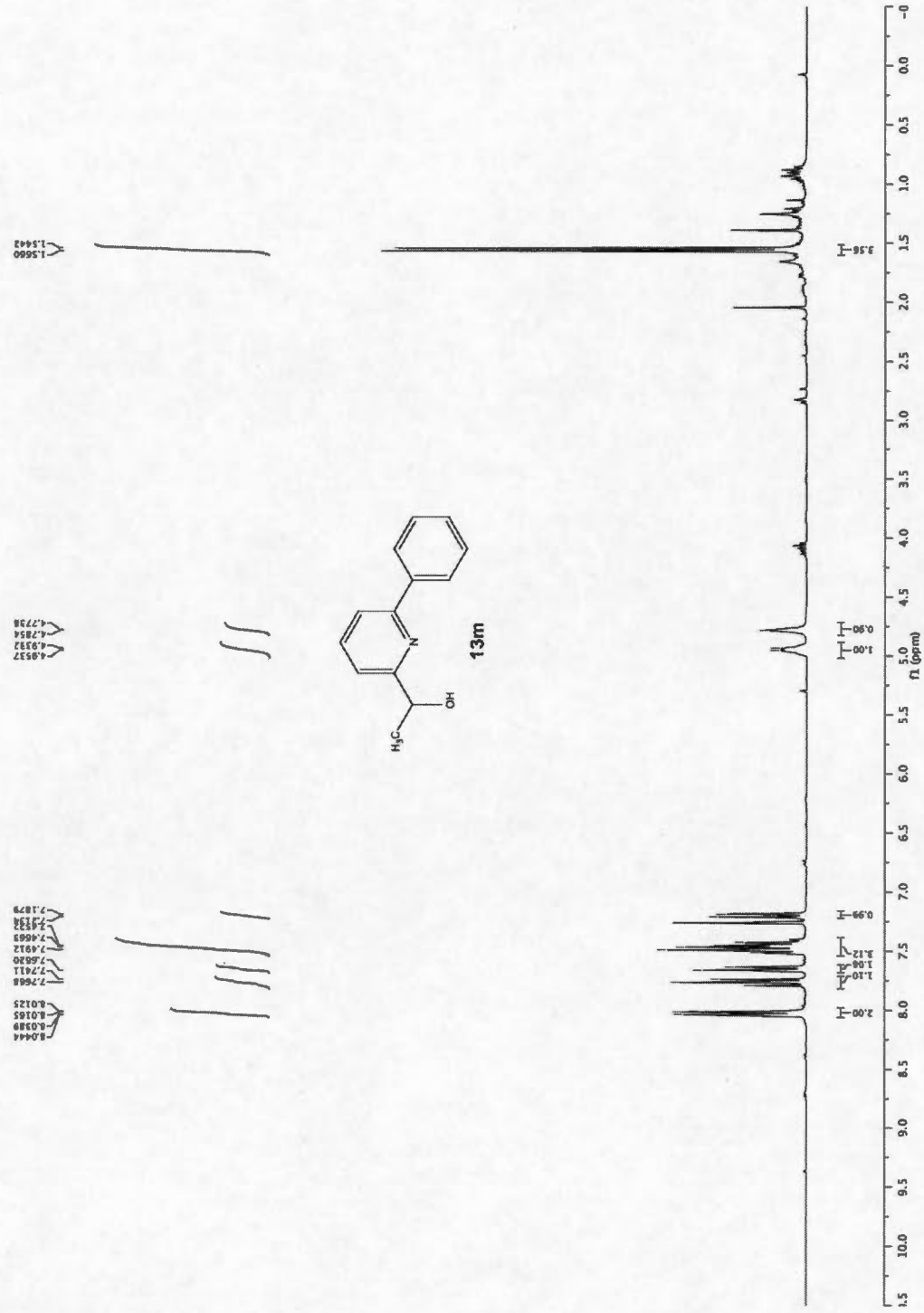

13h
F
F
F
N
f1 (ppm)

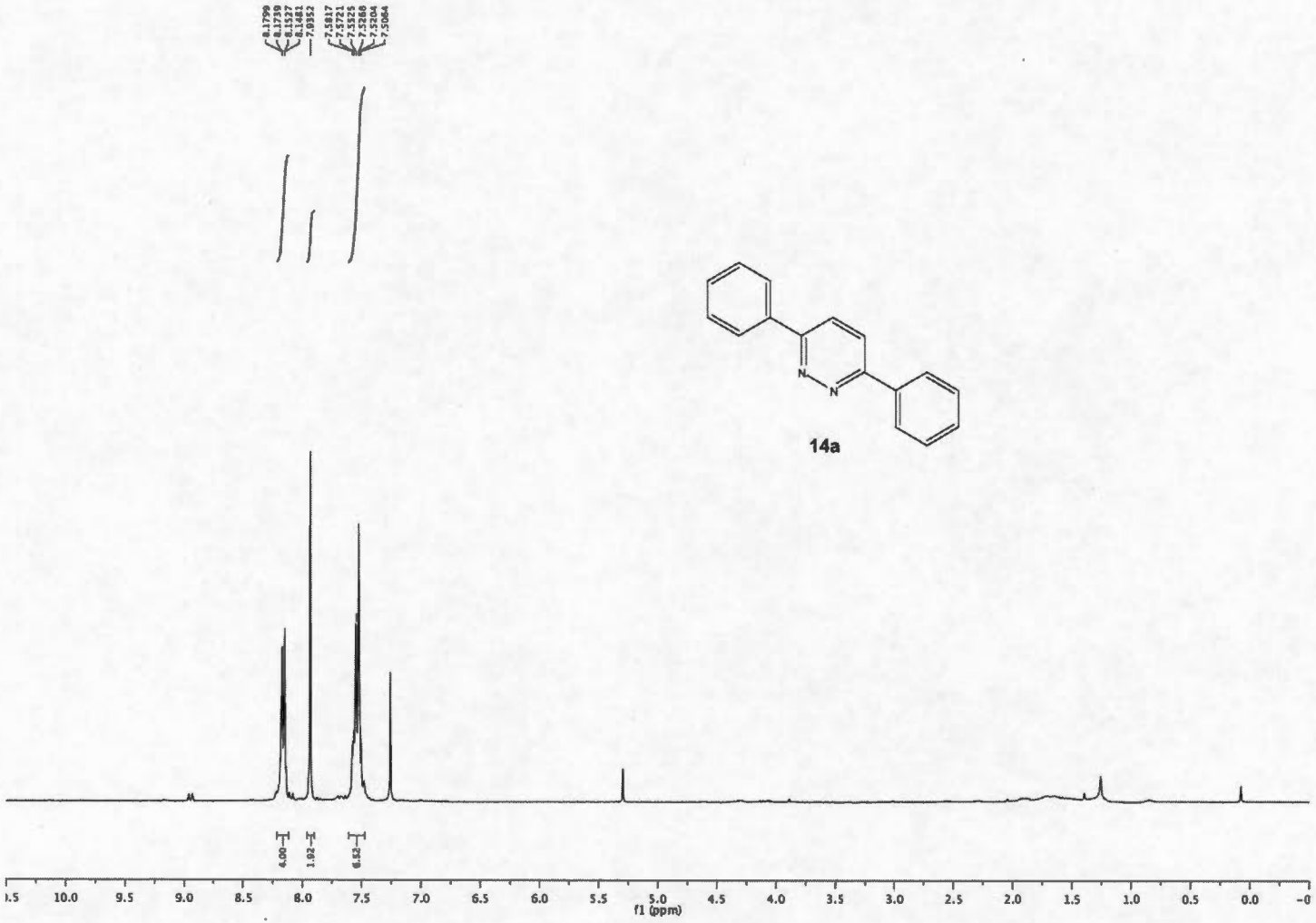

13j
F
F
F
N
8.9525
8.0558
8.0490
8.0291
8.0239
7.9991
7.9927
7.9712
7.9647
7.8587
7.8308
7.5168
7.4964
1.00
3.04
1.01
3.06
f1 (ppm)

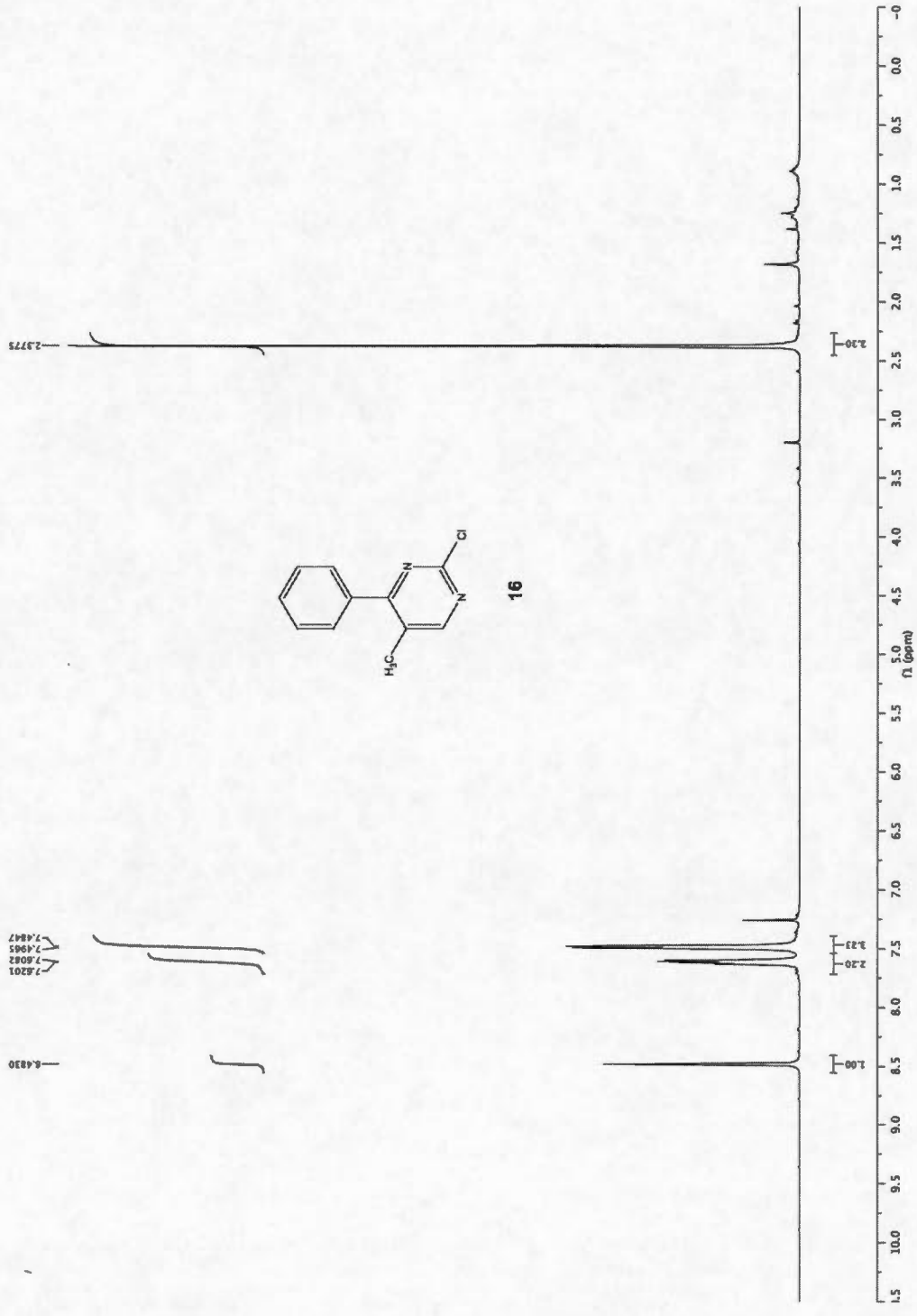

9.4981
8.5442
8.5149
8.5062
8.1058
8.0809
8.0734
7.9267
7.8970
7.5410
7.5186
13k
1.00
1.02
2.15
1.13
9.33
f1 (ppm)

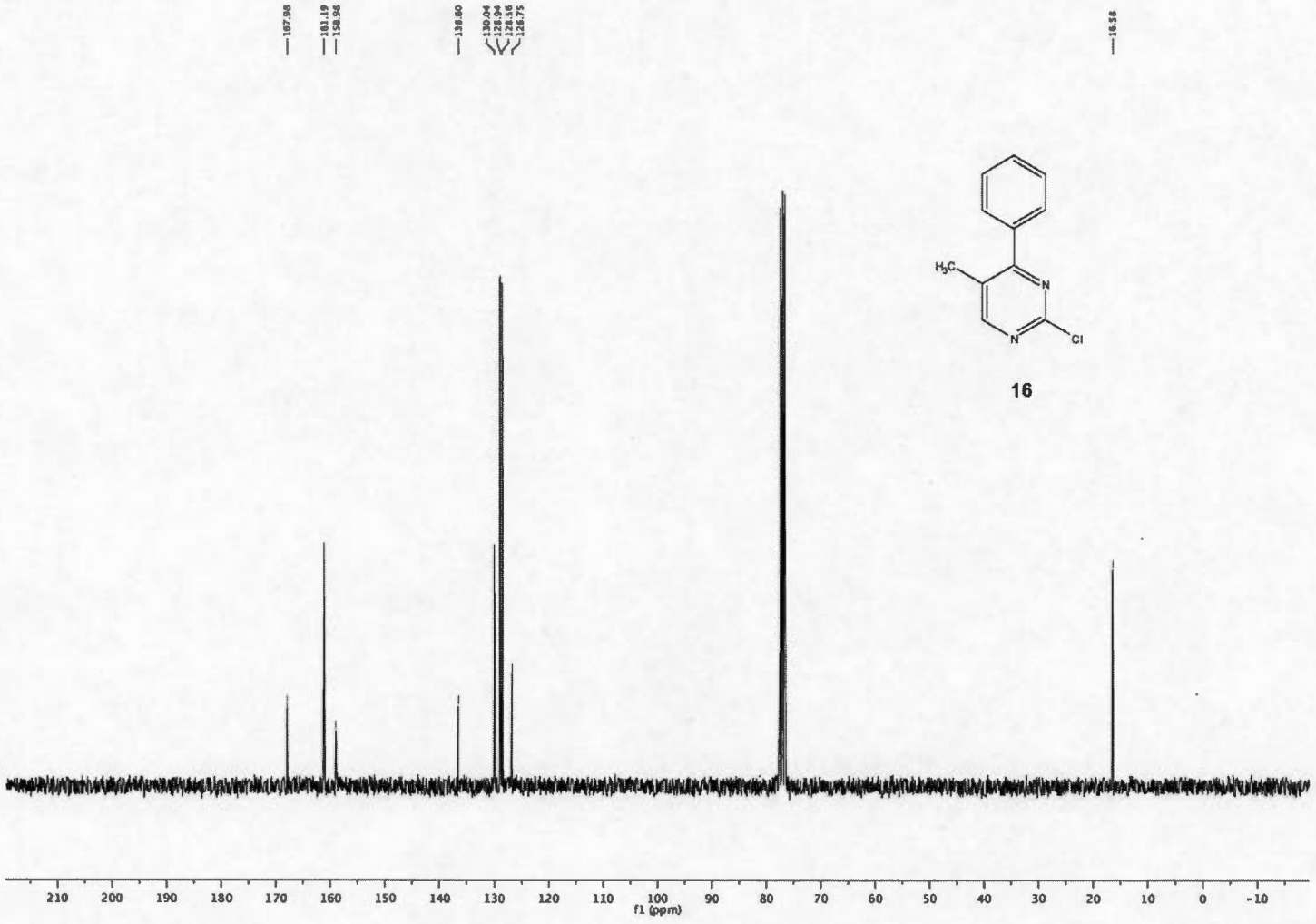

13l
f1 (ppm)

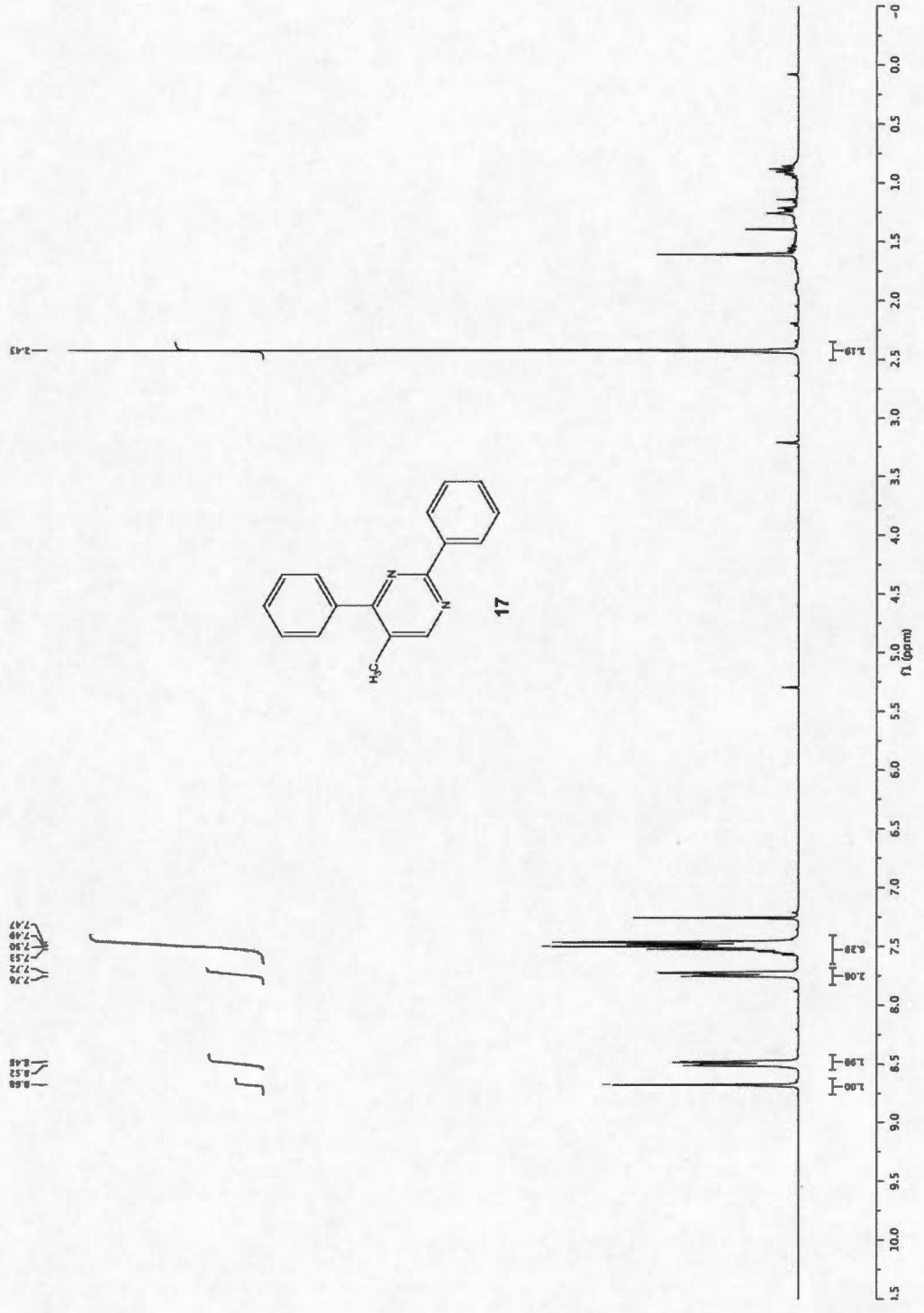

131
N
N
160.52
152.48
140.48
137.38
130.65
129.10
127.40
120.01
117.02
107.89
f1 (ppm)

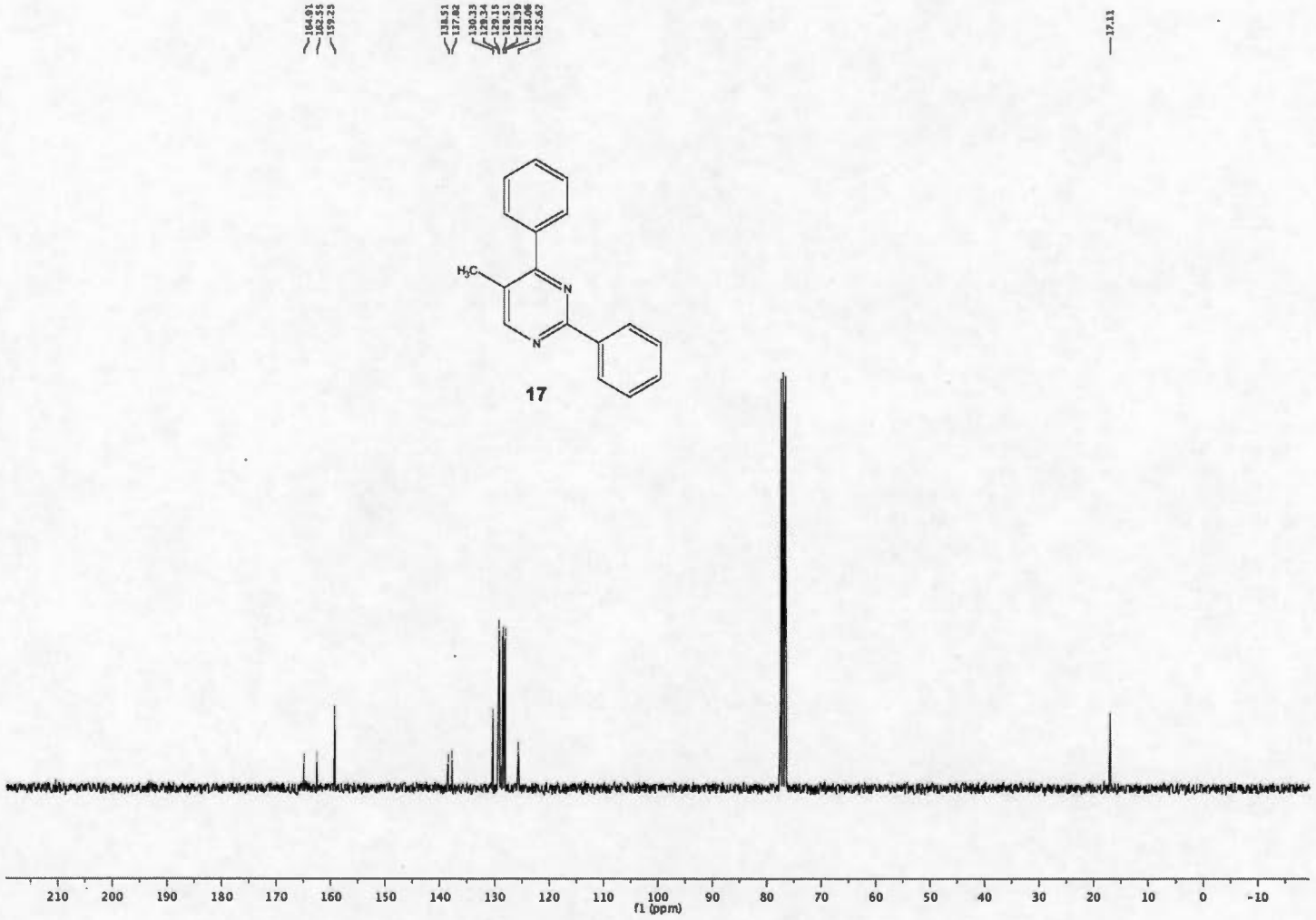

13m
OH
N
H3C
f1 (ppm)

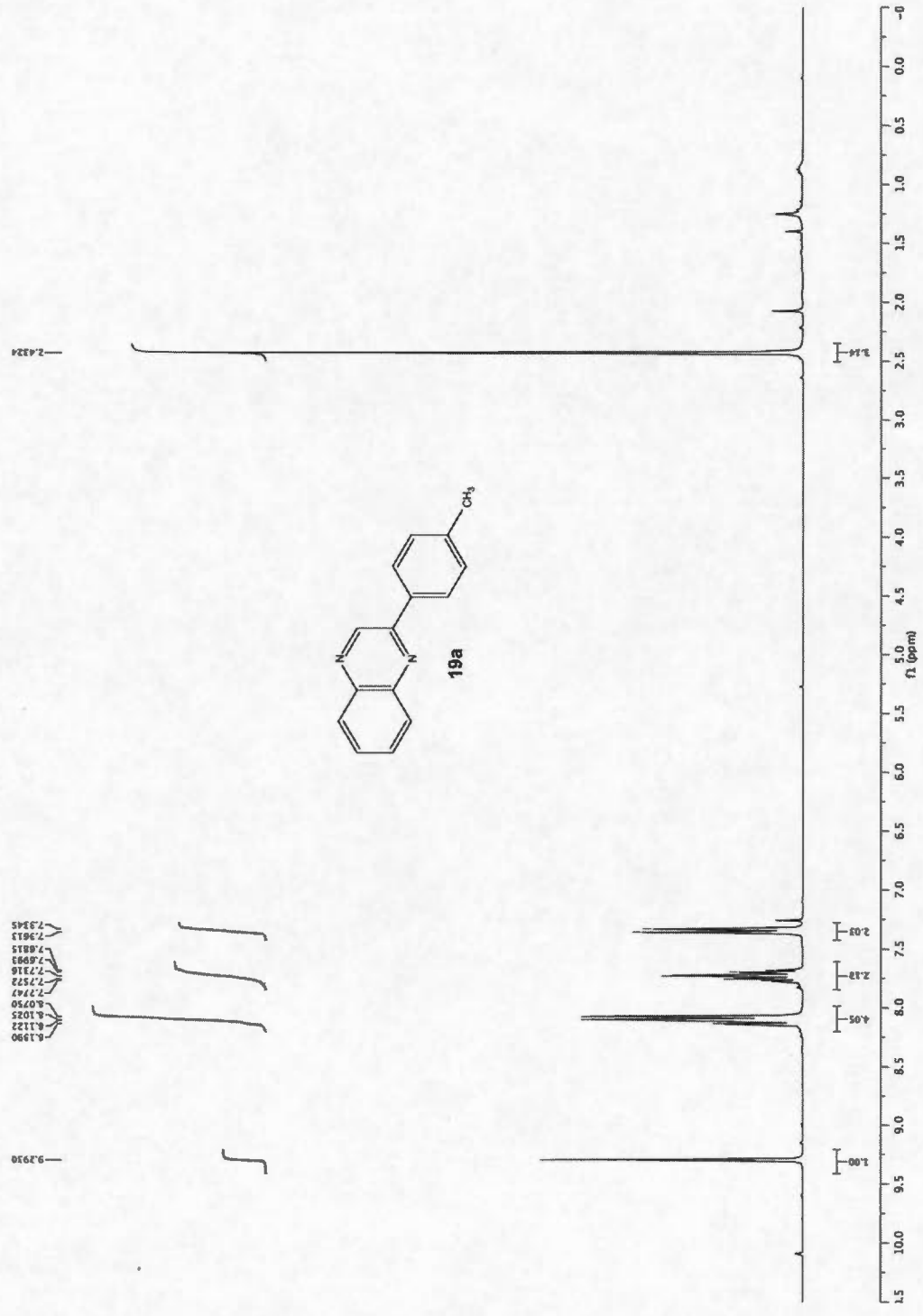

8.1799
8.1730
8.1527
8.1481
7.9552
7.5817
7.5721
7.5525
7.5286
7.5204
7.5064
14a
4.00
1.92
6.53
f1 (ppm)

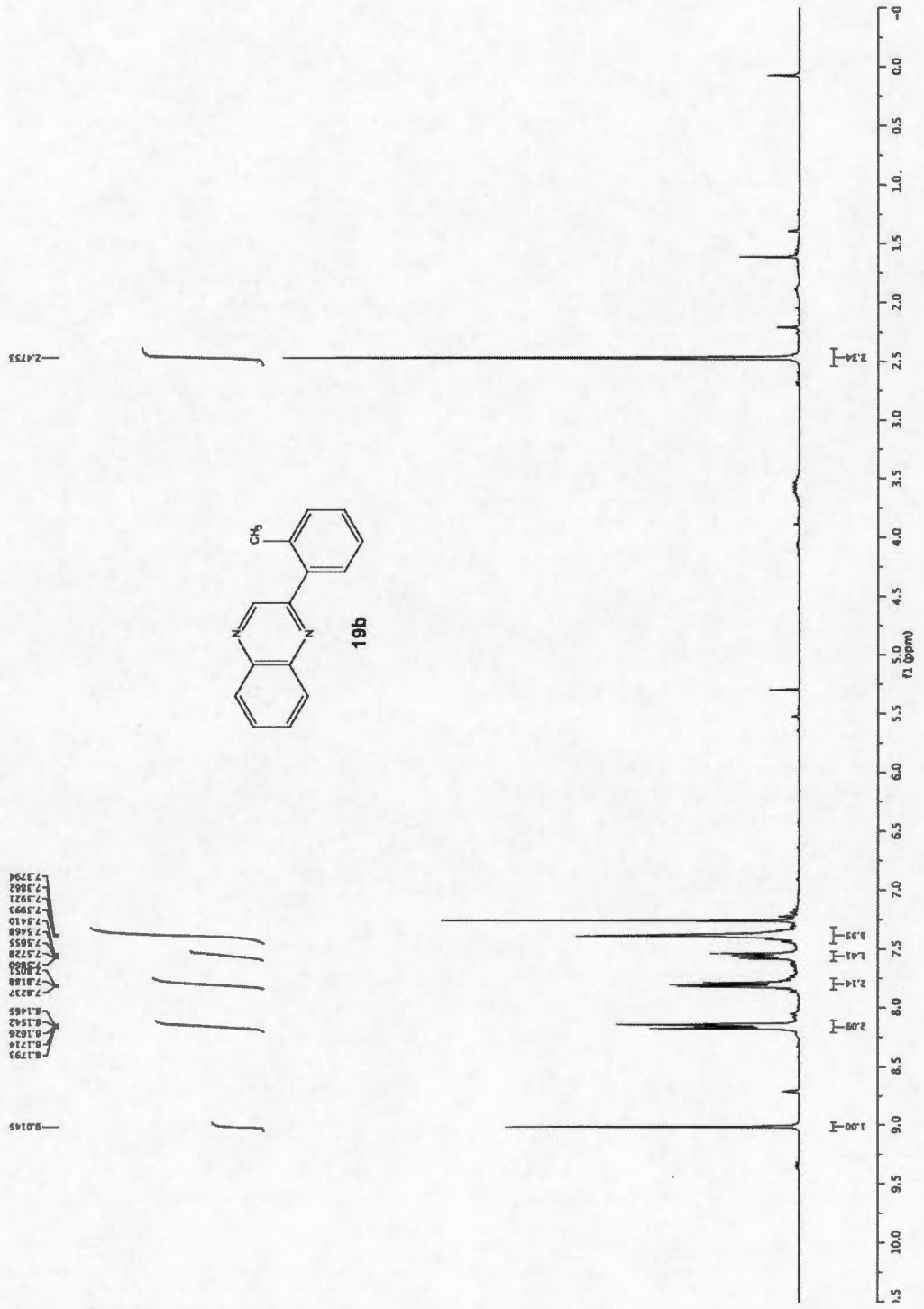

2.5775
6.4830
7.8201
7.8082
7.4965
7.4847
2.30
3.33
2.20
1.00
f1 (ppm)
16

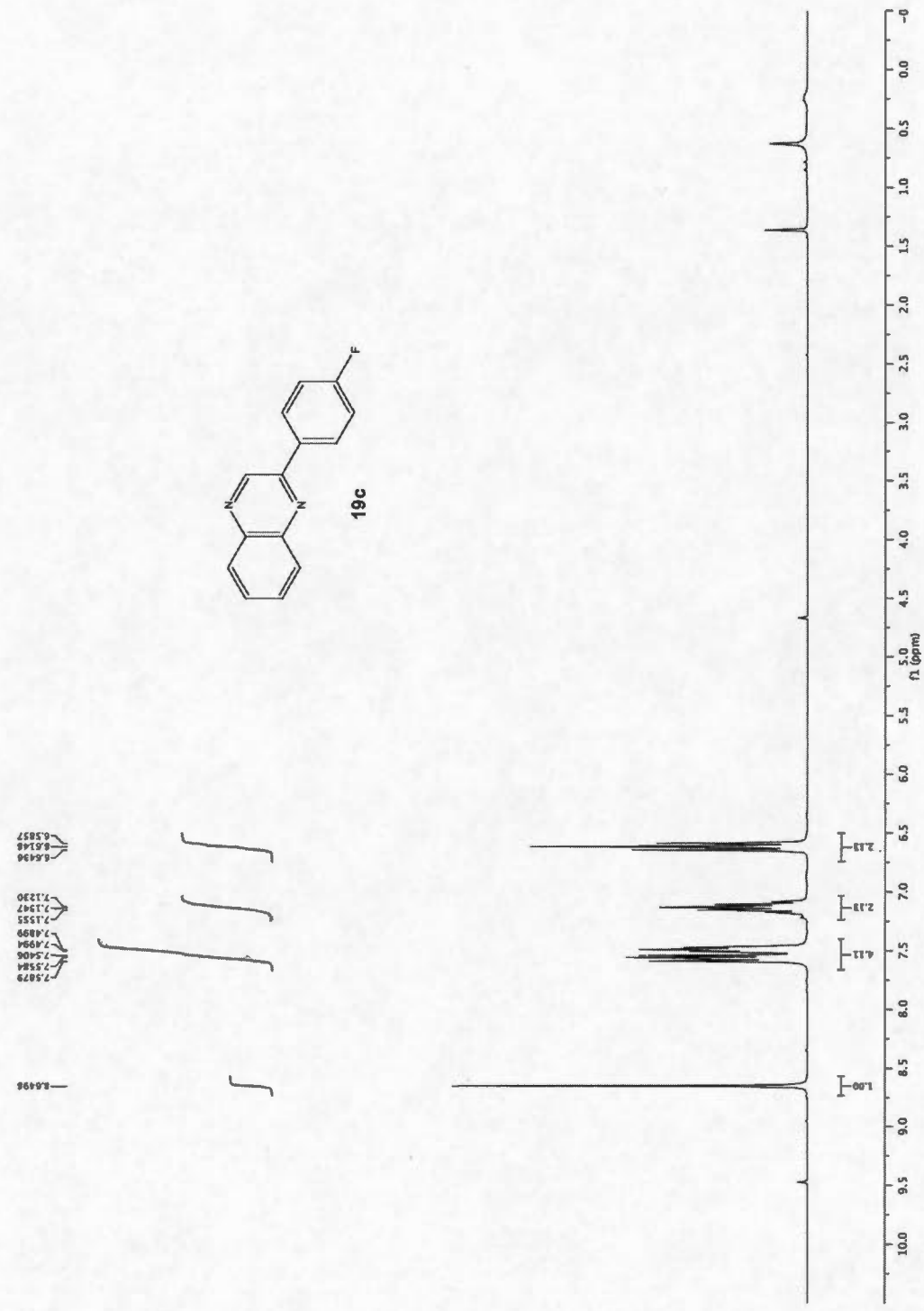

167.98
161.19
158.96
136.80
130.04
128.94
128.16
126.75
16.56
H3C
N
N
Cl
16
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

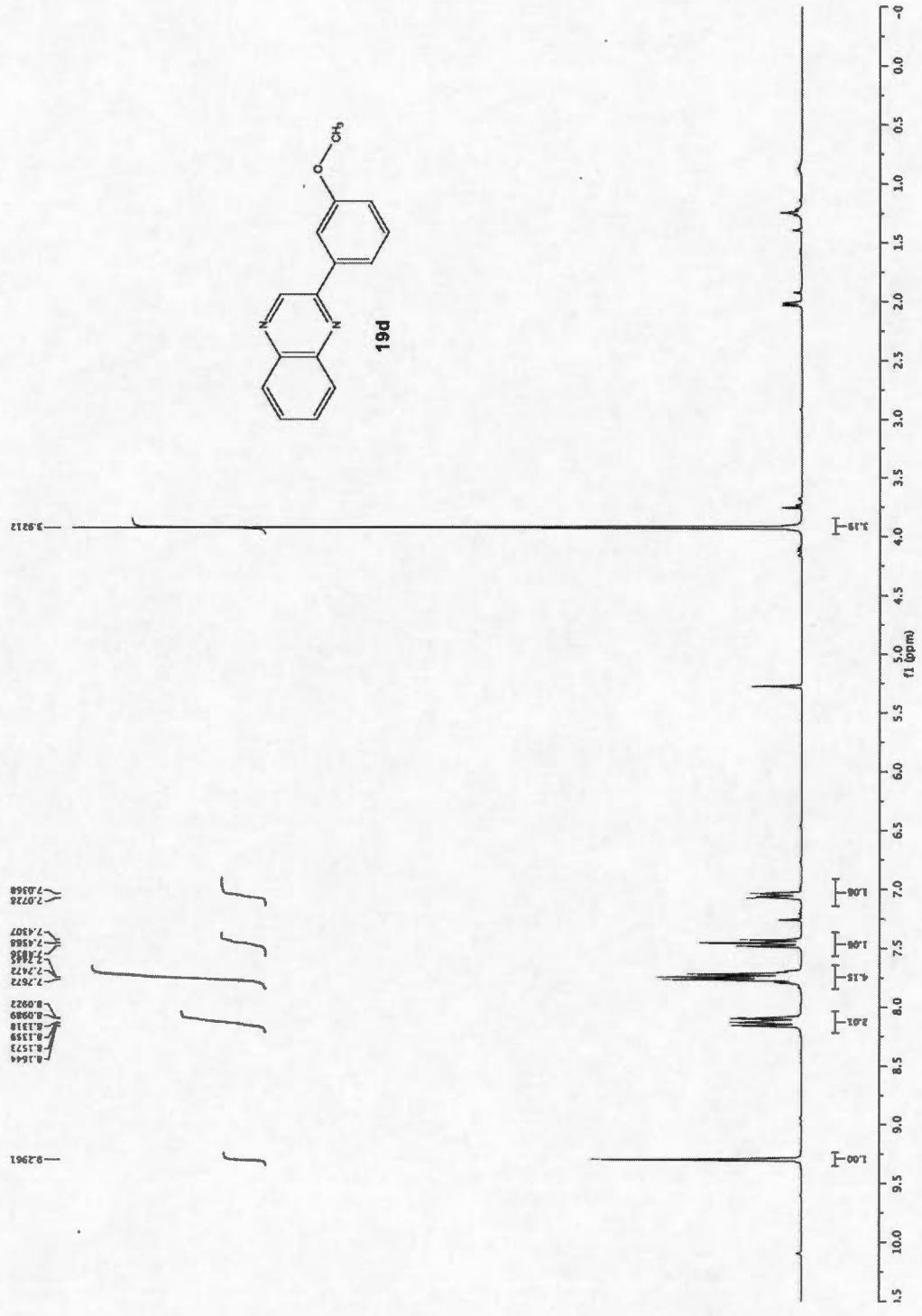

17
f1 (ppm)

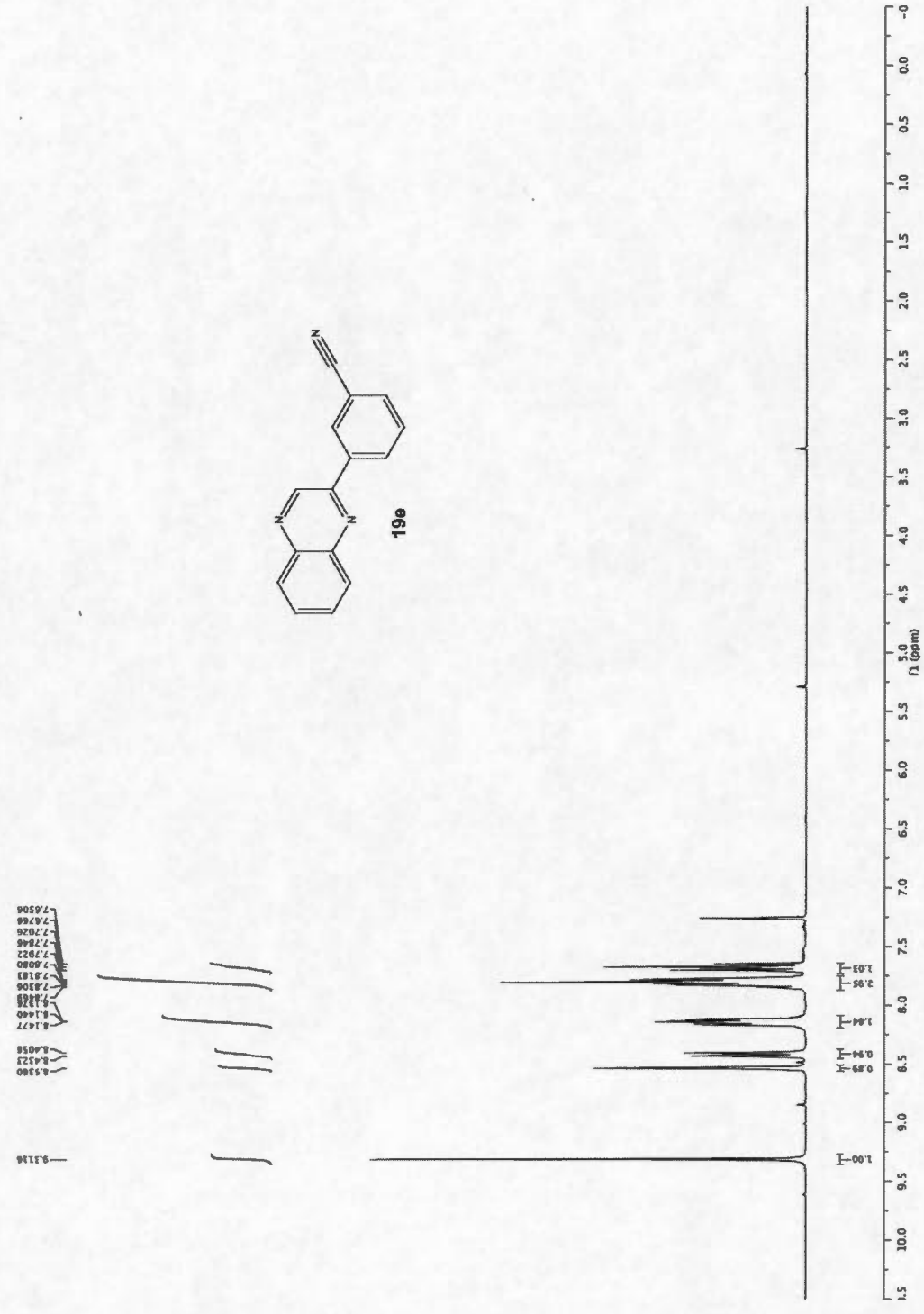

164.91
162.55
159.23
138.51
137.82
130.33
129.34
129.15
128.51
128.39
128.06
125.62
17.11
H3C
N
N
17
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

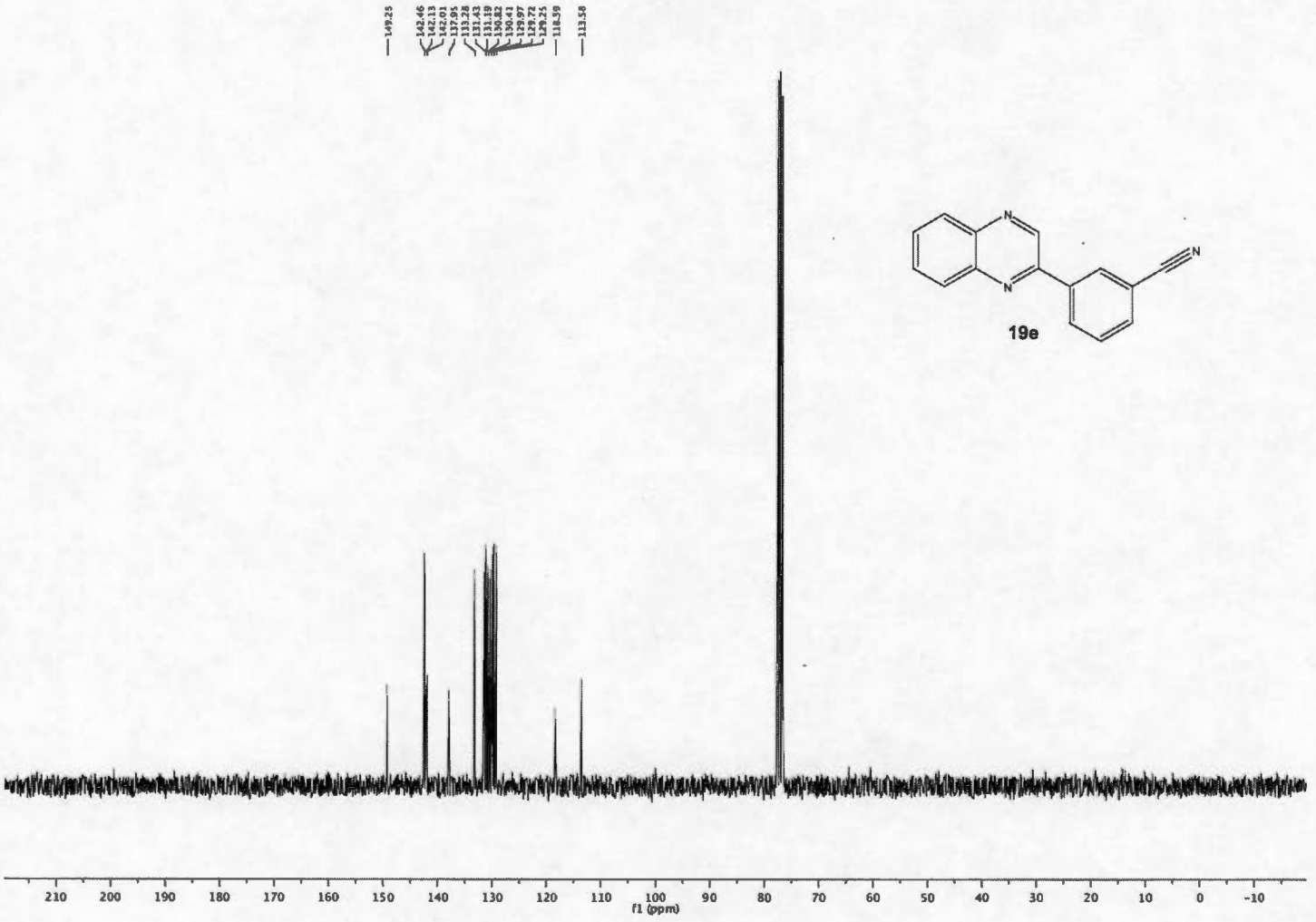

19a
f1 (ppm)

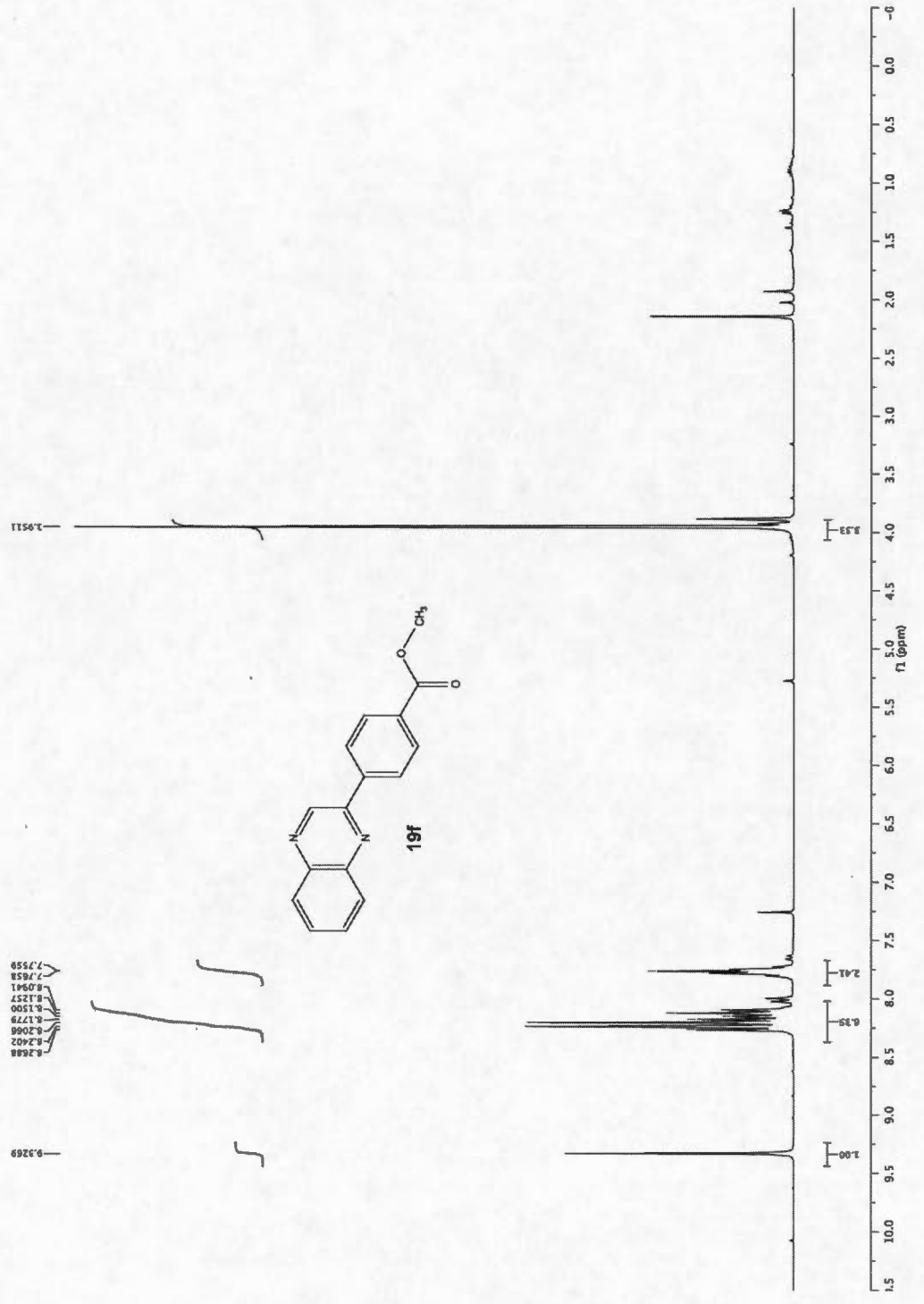

19b
CH3
N
N
(f1 ppm)

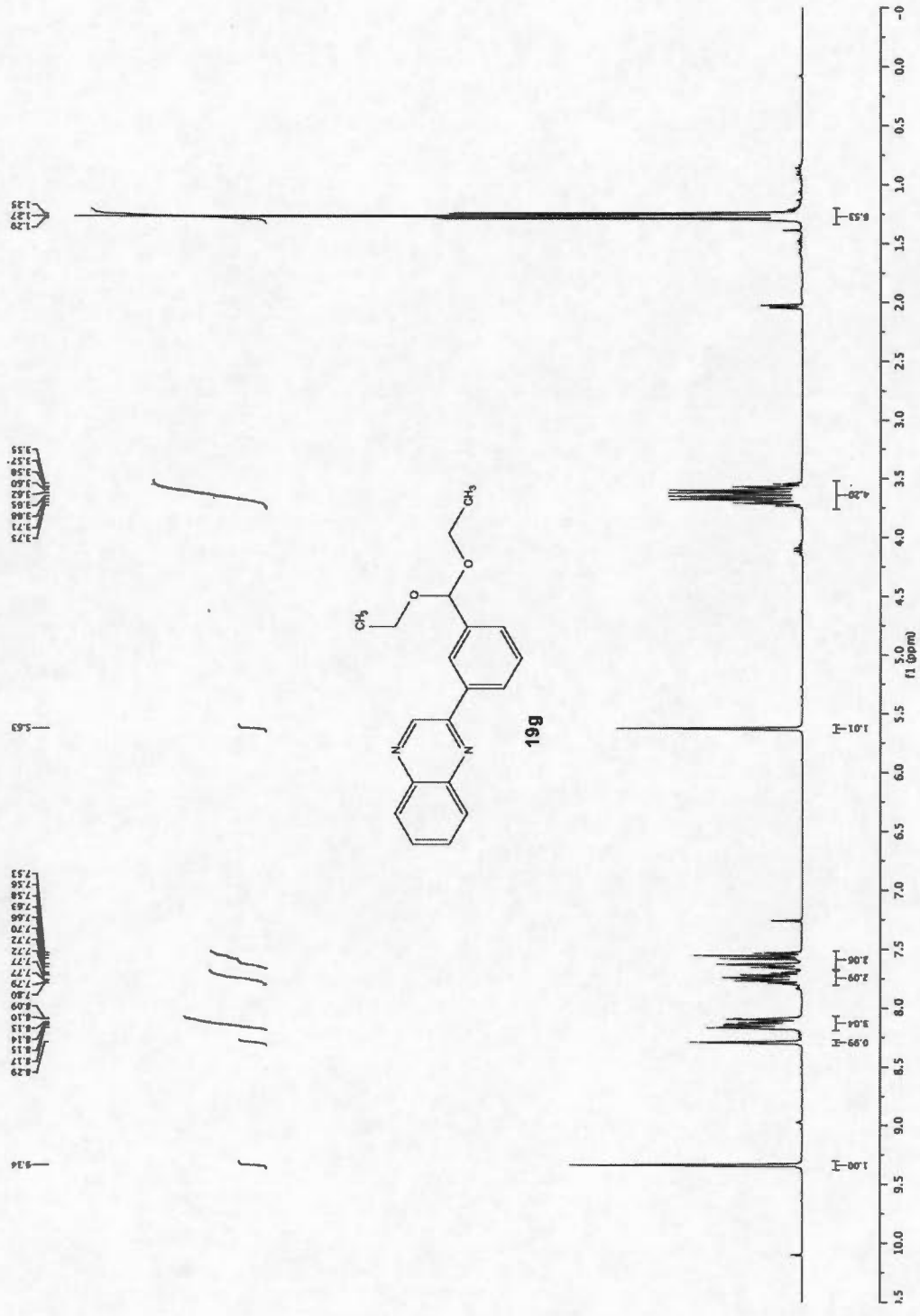

F
N
N
19c
8.6496
8.6496
8.6146
8.5857
7.5079
7.5584
7.5406
7.4994
7.4899
7.1355
7.1347
7.1230
1.00
4.11
2.13
2.13
f1 (ppm)


19d
f1 (ppm)


19e
f1 (ppm)


149.25
143.46
142.13
142.01
137.95
133.28
131.43
131.19
130.82
130.41
129.97
129.72
129.25
118.39
113.58
N
N
N
19e
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


19f
f1 (ppm)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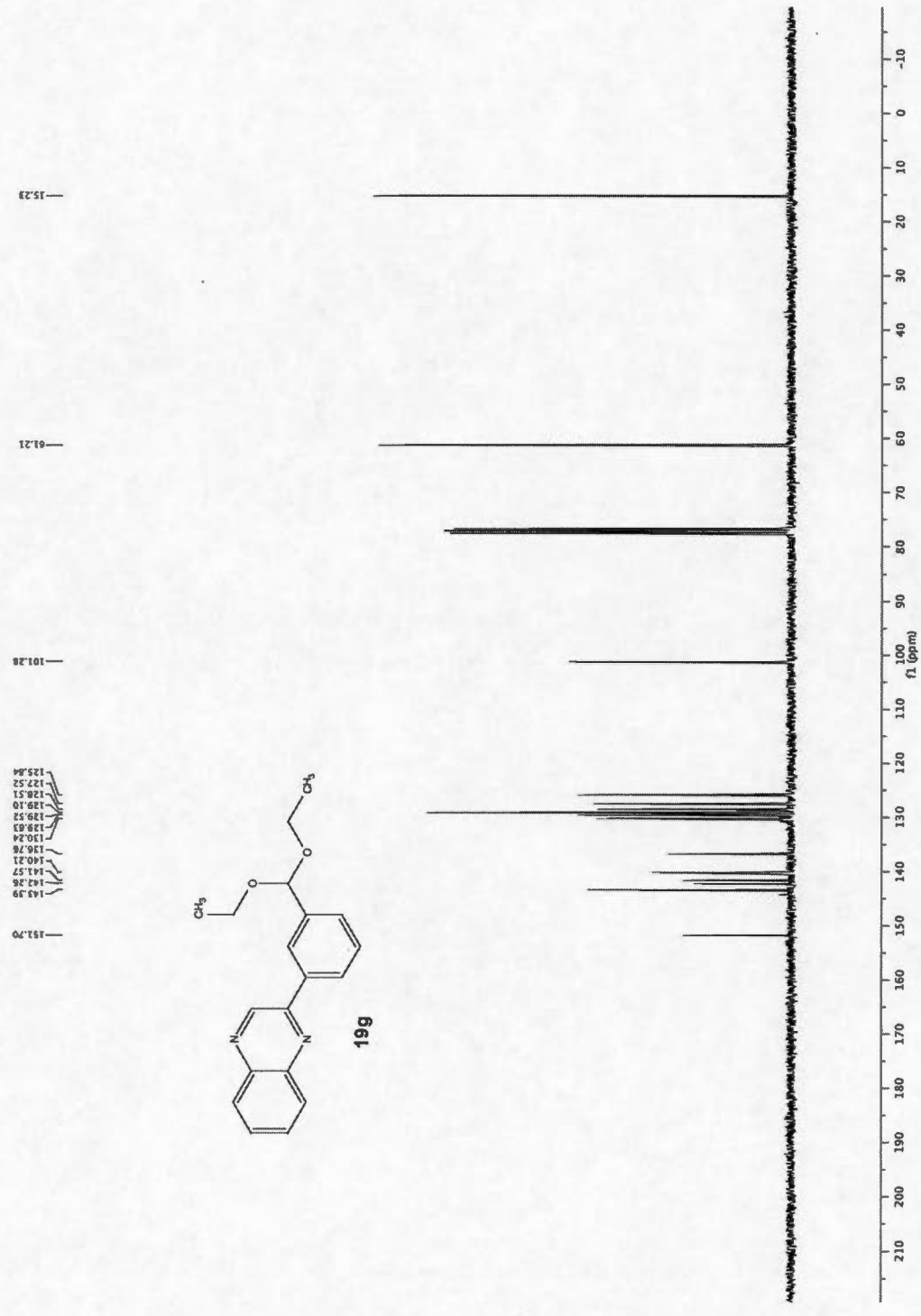
f1 (ppm)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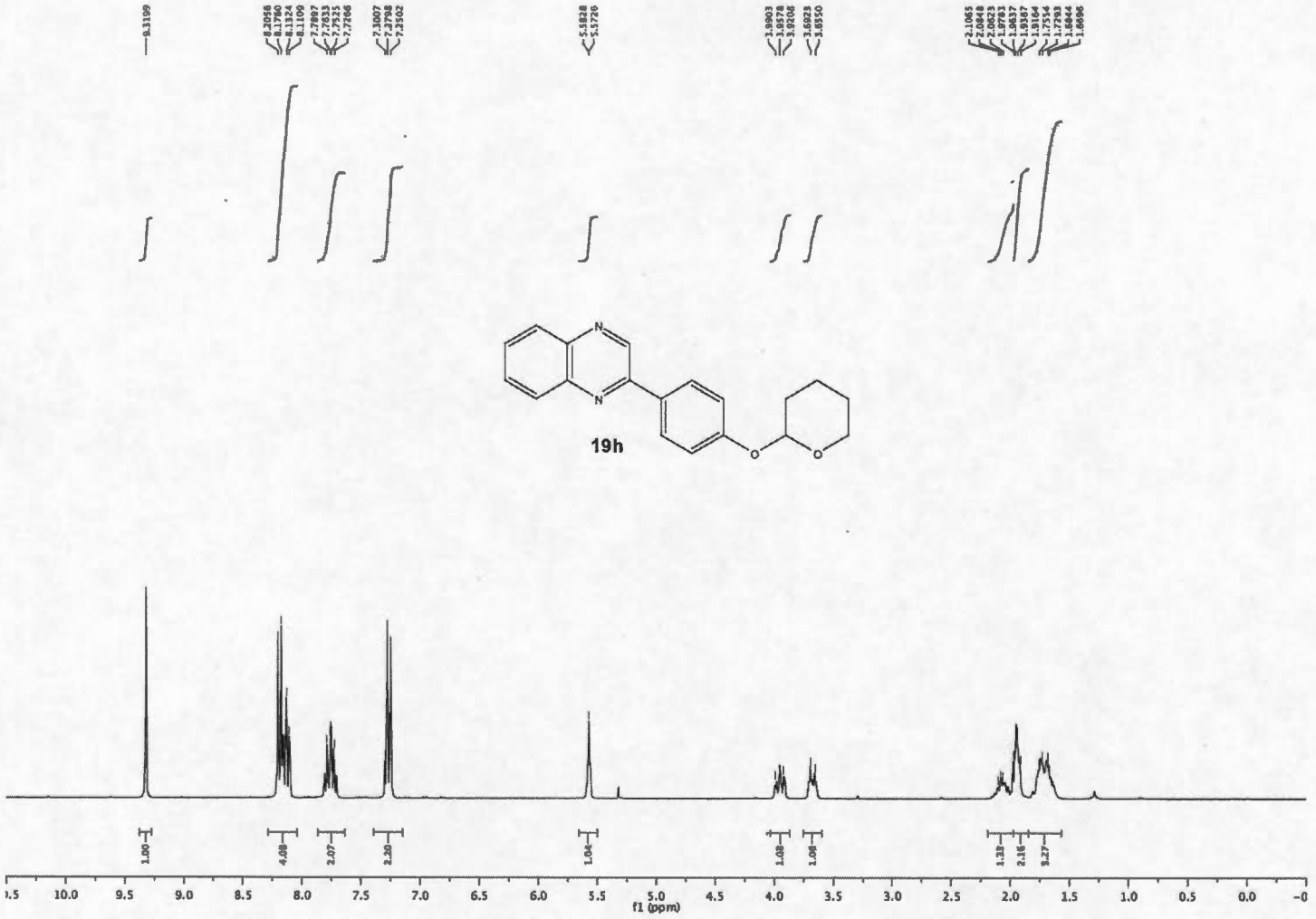
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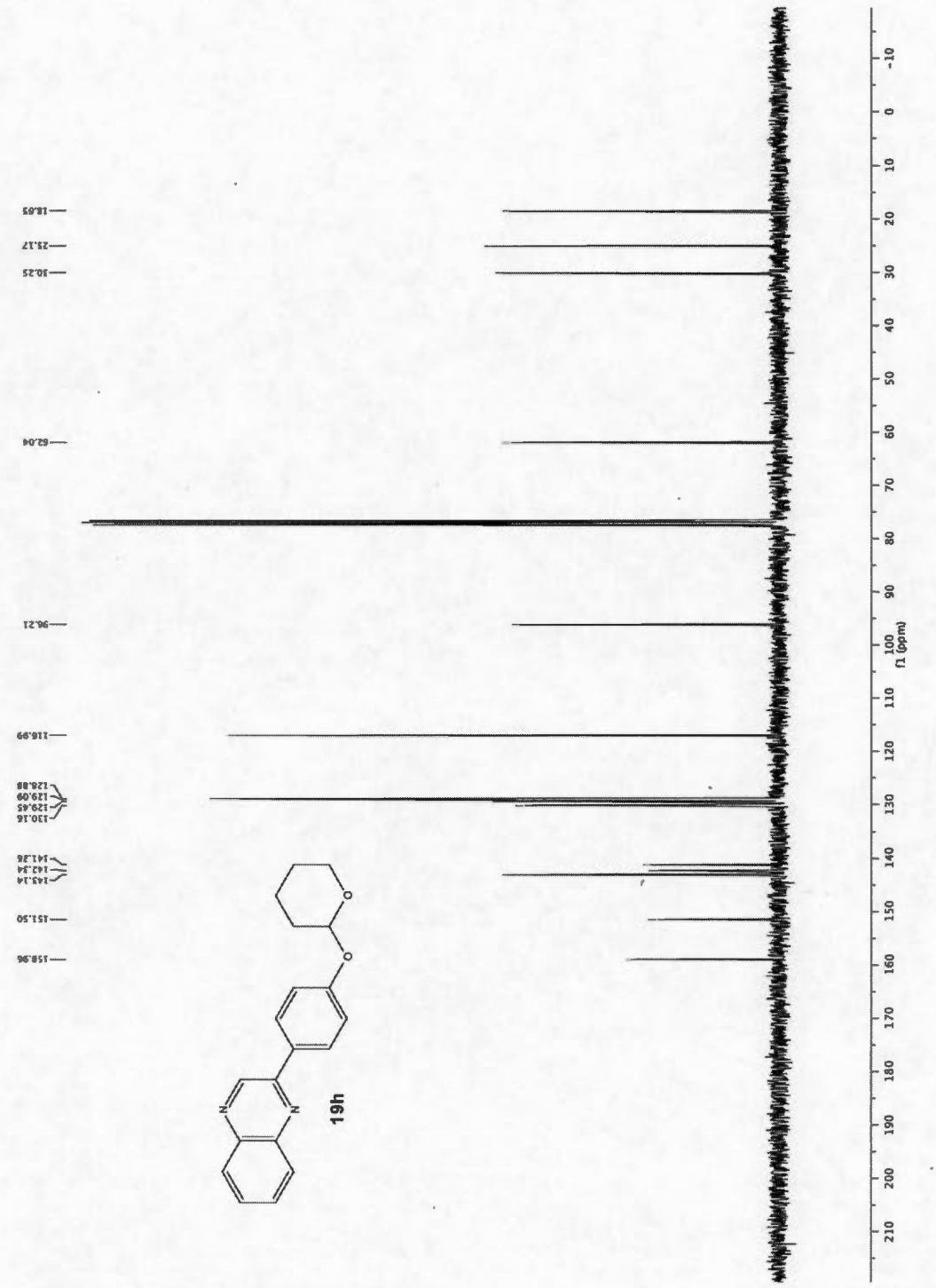
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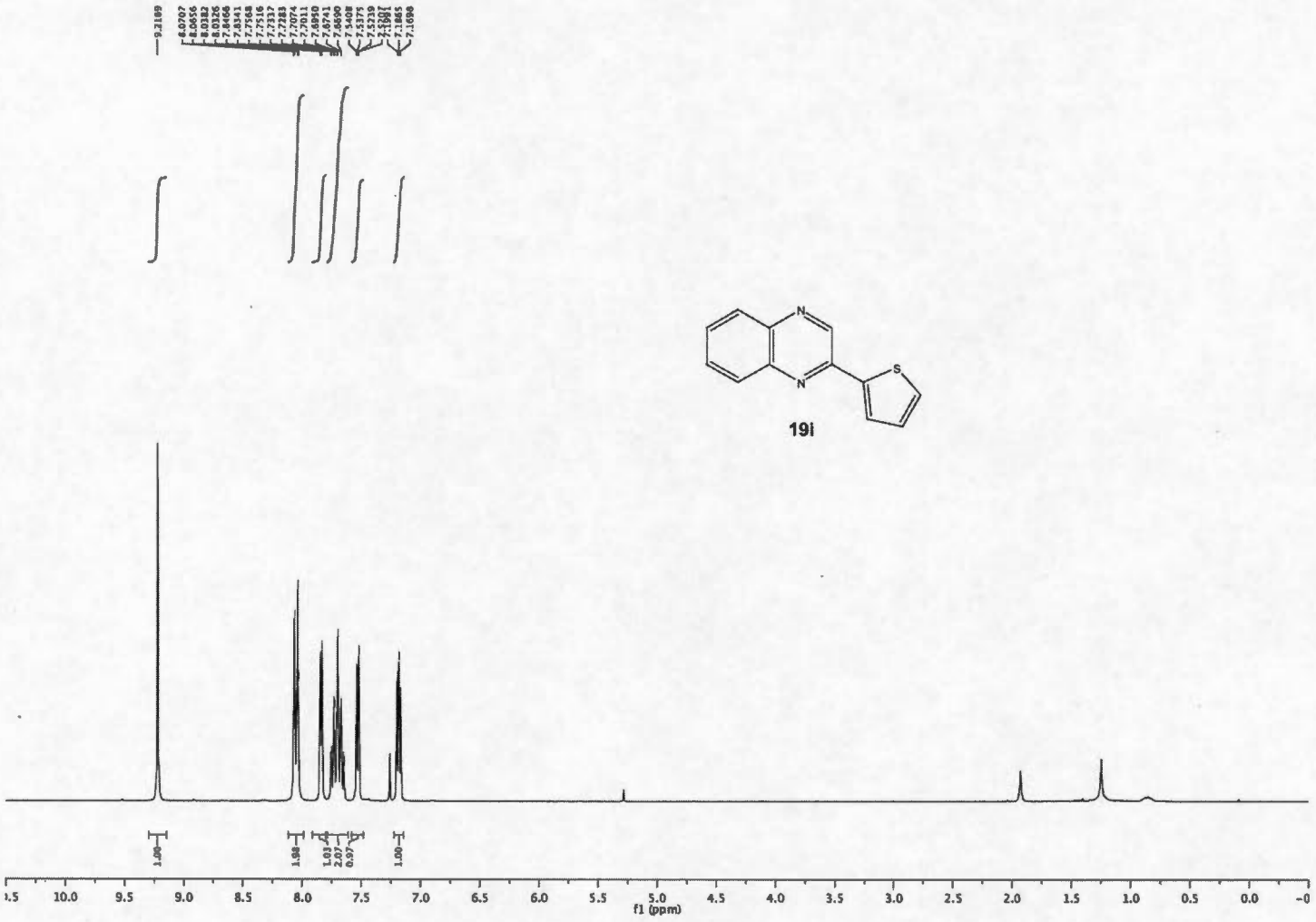
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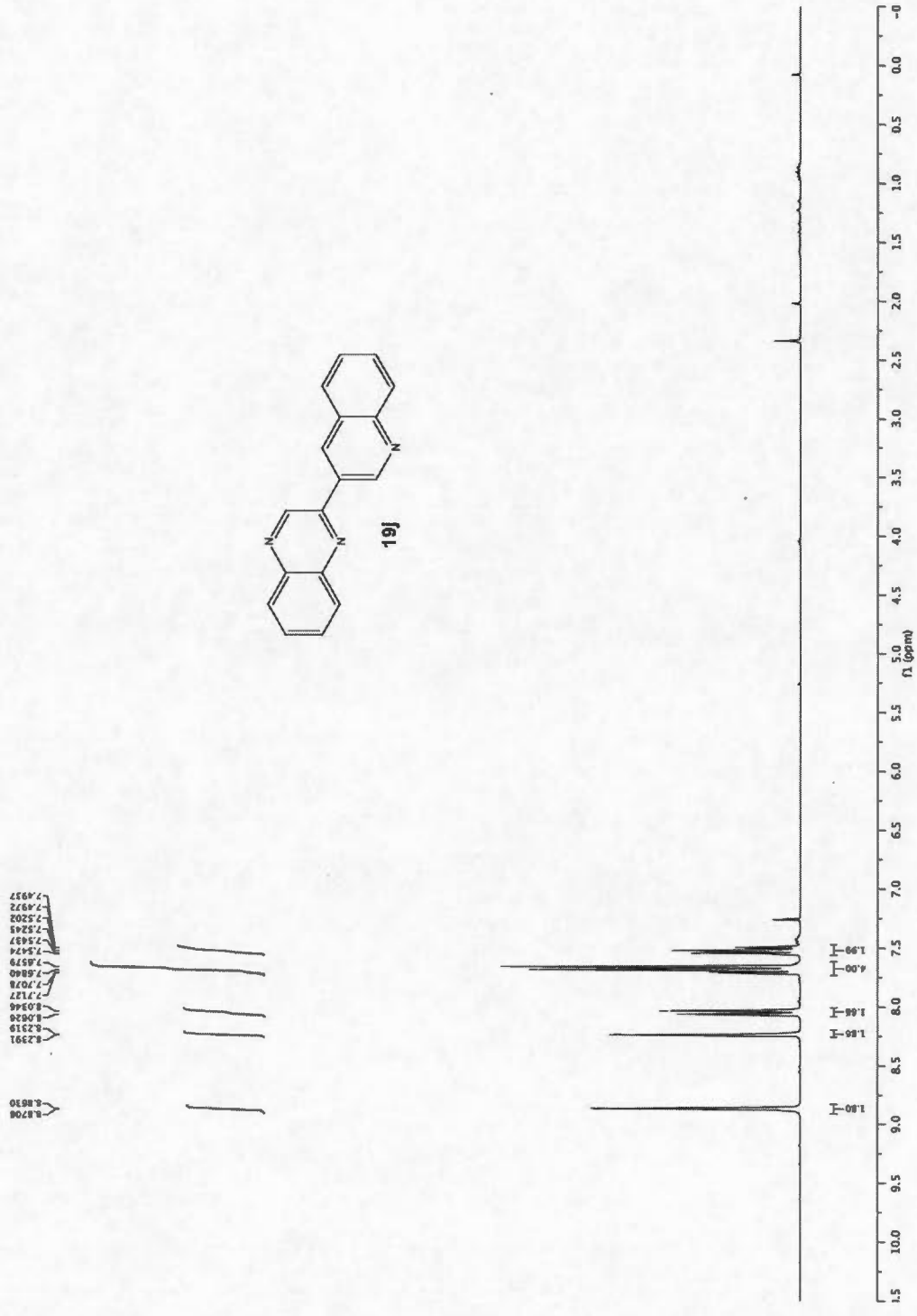
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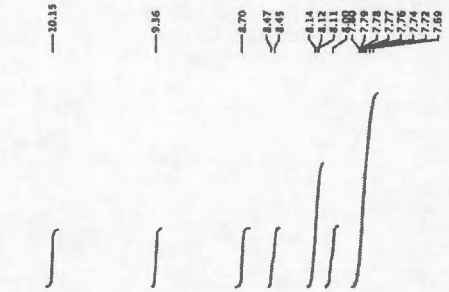
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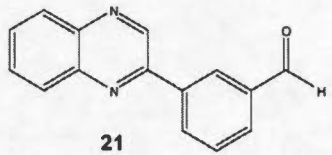
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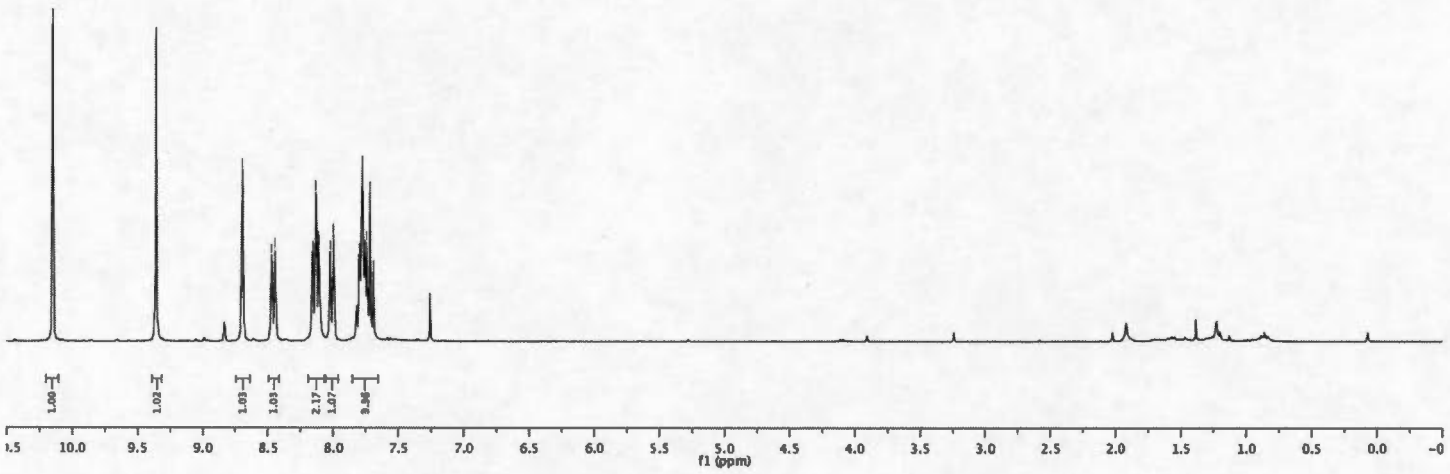
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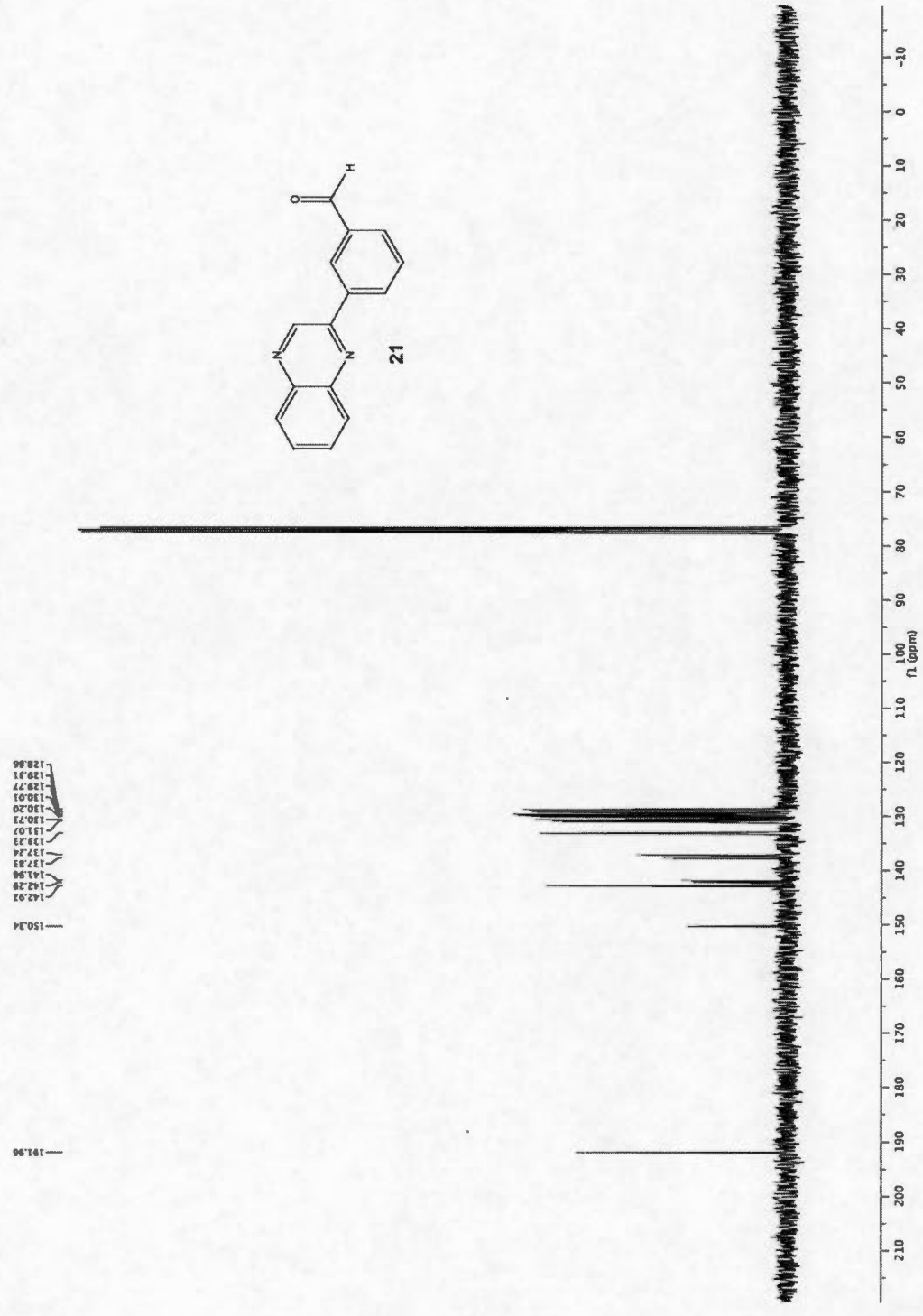
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ANNEXE E

"COPPER-CATALYZED *N*-ARYLATION OF AZOLES AND DIAZOLES USING HIGHLY FUNCTIONALIZED TRIVALENT ORGANOBISMUTH REAGENTS"
ARTICLE

RSC Adv. **2014**, 22255

DOI : 10.1039/c4ra02467b

Titre : Copper-Catalyzed *N*-Arylation of Azoles and Diazoles Using Highly Functionnalized Trivalent Organobismuth Reagents

Auteurs : Pauline Petiot, Julien Dansereau et Alexandre Gagnon*

RSC Advances

COMMUNICATION

Copper-catalyzed *N*-arylation of azoles and diazoles using highly functionalized trivalent organobismuth reagents†

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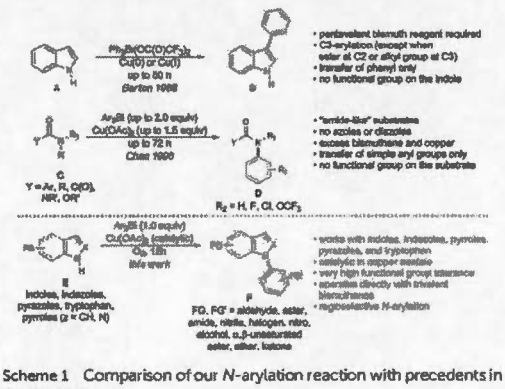
Pauline Petiot, Julien Dansereau and Alexandre Gagnon*

The *N*-arylation of indoles, indazoles, pyrroles, and pyrazoles using highly functionalized trivalent arylbismuth reagents is reported. The reaction is promoted by a substoichiometric amount of copper acetate, and it tolerates a wide diversity of functional groups on the azole and the organobismuth reagent. The method is also applied to the *N*-arylation of tryptophan derivatives.

Azoles and diazoles are common scaffolds that are frequently used in medicinal chemistry to project key pharmacophores along different vectors inside the binding pocket of a biological target.[1,2] *N*-Arylation of these nitrogenated compounds makes it possible to screen for new interactions around an inhibitor[3] and to modify its biophysical properties.[4] *N*-Arylazoles have also found numerous applications in material and polymer sciences.[5] *N*-Arylazoles and diazoles are commonly prepared *via* metal-catalyzed *N*-arylation[6] of N–H heteroarenes using aryl halides,[7] arylboronic acids,[8] or aryllead[9] reagents. However, lead reagents are highly toxic, and other methods sometimes require extended reaction times, super-stoichiometric amounts of catalyst or costly ligands to obtain good yields. Consequently, new procedures that lead to the facile installation of densely functionalized aryl groups on azoles and diazoles are still desirable.

Over the past years, we have disclosed a portfolio of reactions for the formation of C–C,[10] C–N,[11] and C–O[12] bonds using organobismuth reagents. Organobismuthanes can be prepared from inexpensive and non-toxic bismuth salts and offer mild reactivity that tolerates the presence of numerous functional groups on both the substrate and the organometallic species.[13] Barton and Finet reported in 1988 the use of triphenylbismuth-bis-trifluoroacetate in the arylation of indole A (Scheme 1).[14] However, the method was applied exclusively to the transfer of an unsubstituted phenyl group and required the use of a pentavalent bismuth species, which is less stable than its trivalent counterpart. More importantly, C3-arylation was observed in most cases, except when the C3 position was blocked by an alkyl group or when an ester was present at the C2 position of indole.

In 1996, Chan published a variation of a protocol disclosed by Barton and Finet,[15] in which trivalent bismuthanes are used to *N*-arylate nitrogenated compounds (Scheme 1).[16] While this method is very useful, it suffers from multiple limitations as it requires up to 2.0 equivalents of the organobismuth reagent, 1.5 equivalents of the copper catalyst and reaction times that are as long as 72 hours. Moreover, the method was not applied to indoles, indazoles, pyrazoles, or pyrroles, but rather to type C compounds, in which the nitrogen atom is connected to a carbonyl functional group. Finally, functional group tolerance was not demonstrated, as only simple arylbismuthanes were coupled with substrates bearing no functionalities.



Scheme 1 Comparison of our *N*-arylation reaction with precedents in the literature.

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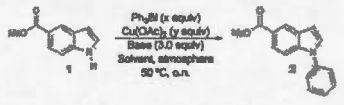
† Electronic supplementary information (ESI) available. CCDC 986210. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ra02467b

We report herein the first method for the *N*-arylation of azoles and diazoles **E** using highly functionalized trivalent bismuth reagents and promoted by catalytic amounts of copper acetate. The procedure exclusively generates the *N*-arylation product and shows exceptional functional group tolerance on both coupling partners. The procedure is also applied to the *N*-arylation of tryptophan derivatives to afford *N*-arylindolyl products.

We began by optimizing the conditions for the phenylation of methyl indole-5-carboxylate **1** using the Barton–Finet–Chan protocol (Table 1).[15,16] Upon reacting 1.0 equivalent of triphenylbismuth with indole **1** in the presence of 1.5 equivalents of copper acetate and 3.0 equivalents of pyridine under air, we obtained the *N*-arylated product **2** regioselectively in quantitative yield (entry 1). This result is interesting and important for two reasons. First, to the best of our knowledge, this is the first time that trivalent organobismuth reagents are used directly in the *N*-arylation of indoles, eliminating the need to prepare the less stable bis-trifluoroacetate species. Second, in contrast with triphenylbismuth-bis-trifluoroacetate, the process involving triphenylbismuth leads exclusively to *N*-arylation, as opposed to C3-arylation. Using 0.7 equivalent of the organobismuth species resulted in a 25% decrease in the yield of the reaction, suggesting that only one phenyl group can be transferred from the organobismuth species during the reaction (entry 2).

In order to develop a more efficient protocol, we next sought to reduce the catalyst loading. Unfortunately, the use of a stoichiometric amount of copper acetate led to a significant decrease in the yield of the reaction (entry 3), motivating us to revisit other parameters of the reaction. Changing the base to triethylamine proved inconsequential (entry 4), but an improvement in the yield of the reaction was observed on conducting the reaction in acetonitrile (entry 5). We recently reported the beneficial effect of oxygen during our studies on the *O*-arylation of phenols using trivalent organobismuthanes.[12] Therefore, we next investigated the use of oxygen as the reaction atmosphere and observed a near quantitative yield for the formation of **2** (entry 6). To further validate the importance of oxygen, we performed the reaction under argon and observed a yield similar to when the reaction was run under ambient air, thus confirming the positive effect of oxygen on the reaction (entry 7 *vs.* 3). Encouraged by this observation, we then gradually lowered the amount of catalyst and found that the yield was retained upon using 10 mol% of copper acetate (entry 8). However, reducing the loading further was not tolerated and produced only a modest yield of the desired *N*-phenyl indole **2** (entry 9). Although Barton reported that the *exclusion* of oxygen led to a negative impact on the arylation of amines with trivalent organobismuthanes,[15] the possibility of lowering the copper acetate loading by performing the reaction under pure oxygen was not demonstrated. It is likely that the role of the oxygen is to oxidize the copper species with lower valency, which are generated during the reaction, to the +2 oxidation state. To minimize the amount of base, we performed the reaction using 1.0 equivalent of pyridine and still obtained a near quantitative yield of product **2** (entry 10). The exploration of non-halogenated solvents (entries 11–13) led to the identification of THF as the best alternative to dichloromethane. Using our optimal conditions, we next explored the impact of varying the steric and electronic properties of the organobismuthane on the yield of the arylation reaction. The functionalized organobismuthanes

Table 1 Optimization of reaction conditions for the *N*-phenylation of methyl-indole-5-carboxylate **1** using triphenylbismuth



Entry	Ph_3Bi (*x* equiv.)	$Cu(OAc)_2$ (*y* equiv.)	Base	Solvent	Atm.	Yield[a] (%)
1	1.0	1.5	Pyridine	CH_2Cl_2	Air	99
2	0.7	1.5	Pyridine	CH_2Cl_2	Air	74
3	1.0	1.0	Pyridine	CH_2Cl_2	Air	45
4	1.0	1.0	Et_3N	CH_2Cl_2	Air	45
5	1.0	1.0	Pyridine	CH_3CN	Air	76
6	1.0	1.0	Pyridine	CH_2Cl_2	O_2	96
7	1.0	1.0	Pyridine	CH_2Cl_2	Ar	47
8	1.0	0.1	Pyridine	CH_2Cl_2	O_2	99
9	1.0	0.05	Pyridine	CH_2Cl_2	O_2	45
10[b]	1.0	0.1	Pyridine	CH_2Cl_2	O_2	96
11	1.0	0.1	Pyridine	THF	O_2	82
12	1.0	0.1	Pyridine	DME	O_2	57
13	1.0	0.1	Pyridine	CH_3CN	O_2	54

[a] Isolated yield of pure product **2**. [b] Reaction performed with 1.0 equiv. of base.

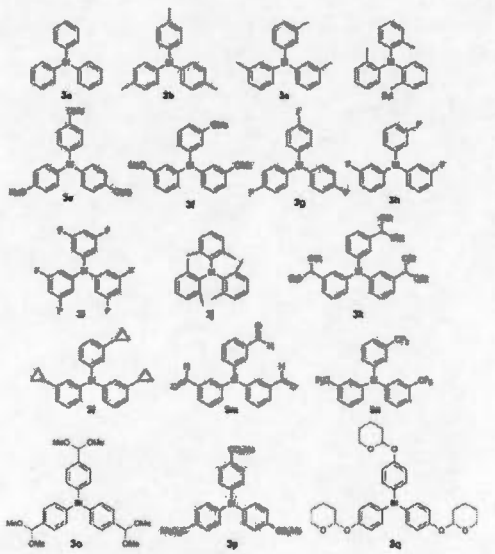


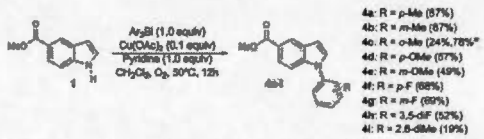
Fig. 1 Functionalized organobismuthanes **3a–q** used in the *N*-arylation of azoles and diazoles.

needed for this study (Fig. 1) were prepared according to procedures that we previously reported.[10b,12]

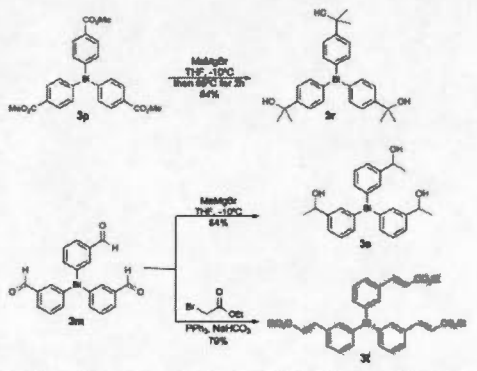
Our studies show that the transfer of *para* and *meta*-tolyl groups proceeds efficiently, delivering the corresponding products **4a** and **4b** in excellent yields (Scheme 2). The transfer of the more sterically hindered *ortho*-tolyl group proved more challenging and required a higher catalyst loading to provide the desired product **4c** in an acceptable yield. While it is difficult to establish a clear correlation between the electronic properties of the organobismuthane and the yield of the arylation reaction, the results obtained to date demonstrate that good yields are afforded by using triarylbismuthanes substituted with electron-donating (**4a, b, d**) and electron-withdrawing (**4e–h**) groups. Interestingly, a 2,6-dimethylphenyl unit was installed on indole **1** using our conditions, although with a modest yield (compound **4i**). Note that very few methods exist for the transfer of this highly hindered group.[17]

In order to further expand the functional group tolerance, we prepared three new bismuth reagents by performing a functional group manipulation directly on selected organobismuthanes. As illustrated in Scheme 3, triarylbismuthanes **3r** and **3s**, bearing alcohol functional groups, were synthesized by Grignard addition on the ester **3p** and on the aldehyde **3m**, respectively. These groups are important in medicinal chemistry as the presence of an alcohol group controls the lipophilicity (log *D*) of arylated products that are generated in the next step. A Horner–Emmons–Wadsworth reaction was also performed on **3m** to furnish the cinnamyl ester **3t**. This functional group is also frequently found in numerous bioactive compounds.

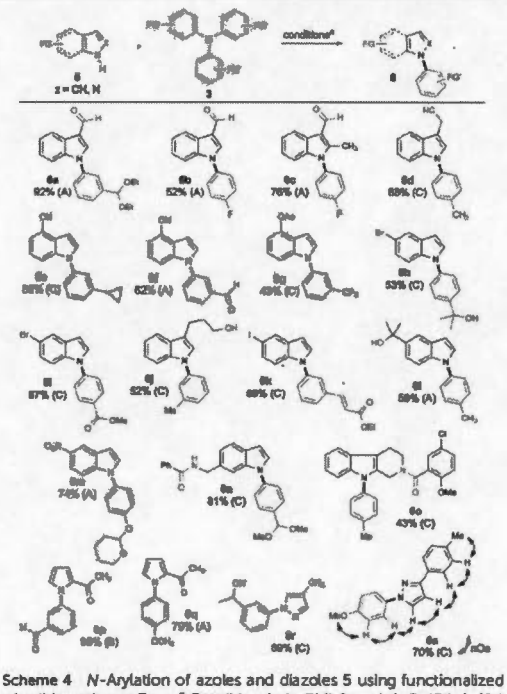
The scope of the reaction was then studied by arylating different azoles and diazoles **5** using highly functionalized triarylbismuthanes **3a–t** (Scheme 4). Our investigations reveal that the reaction proceeds smoothly on indoles (**6a–o**), pyrroles (**6p, q**), and pyrazoles[18] (**6r, s**) to afford the desired *N*-arylated products in good to excellent yields. These results also suggest that the substitution pattern of the indole has little impact on the outcome of the reaction. However, using our conditions, we were not able to arylate 7-methylindole, possibly due to the development of a strong 1,3-allylic-type strain during the formation of the product. In the case of pyrazole **6s**, the product of arylation on the nitrogen distal to the tolyl group was obtained, as confirmed by NMR studies. Importantly, the procedure tolerates a wide variety of functional groups on the azole such as aldehydes (**6a–c**), nitriles (**6d–f**), *O*-acetates (**6g**), nitro groups (**6m**), amides (**6n, o**), and ketones (**6p, q**). Note that



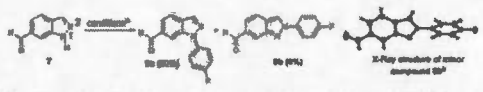
Scheme 2 Steric and electronic effects of organobismuthane on the *N*-arylation of **1**. [a] Alternative conditions were employed for compound **4c**: Ar_3Bi (1.0 equiv.), $Cu(OAc)_2$ (1.0 equiv.), pyridine (3.0 equiv.), CH_2Cl_2, O_2, 50 °C, 12 h.



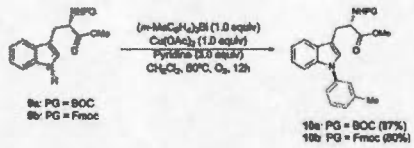
Scheme 3 Preparation of highly functionalized organobismuthanes by functional group manipulation.



Scheme 4 *N*-Arylation of azoles and diazoles **5** using functionalized triarylbismuthanes **3a–t**. [a] Condition A: Ar_3Bi (1.0 equiv.), $Cu(OAc)_2$ (0.1 equiv.), pyridine (1.0 equiv.), CH_2Cl_2, O_2, 50 °C; condition B: Ar_3Bi (1.0 equiv.), $Cu(OAc)_2$ (0.1 equiv.), pyridine (3.0 equiv.), CH_2Cl_2, O_2, 50 °C; condition C: Ar_3Bi (1.0 equiv.), $Cu(OAc)_2$ (1.0 equiv.), pyridine (3.0 equiv.), CH_2Cl_2, O_2, 50 °C.



Scheme 5 *N*-Arylation of 1*H*-indazole-6-carbaldehyde 7. [a] Conditions: (p-$FC_6H_4)_3Bi$ (1.0 equiv.), $Cu(OAc)_2$ (1.0 equiv.), pyridine (3.0 equiv.), DCM, 50 °C, O_2, o.n.; [b] ORTEP diagram of compound 8b: thermal ellipsoids are shown at the 50% probability level.



Scheme 6 *N*-Arylation of tryptophan derivatives 9a, b.

bromides (6h, i), and iodides (6k), which could be expected to interfere in the direct *N*-arylation of azoles with aryl halides, were found to be inert under these conditions. Numerous functional groups can also be present on the organobismuth reagents, such as acetals (6a, m, n), fluorides (6b, c), aldehydes (6f, p), esters (6l), ethers (6q, s) and α,β-unsaturated esters (6k). Interestingly, we found that an alcohol can be present on the substrate (6j, l) or on the arylbismuth reagent (6r) without undergoing *O*-arylation; moreover, a secondary amide is not arylated under these conditions (6n). Lastly, a cyclopropylphenyl (6e) and a trifluoromethylphenyl (6g) group were efficiently transferred using this method. These groups are important in medicinal chemistry as they show increased metabolic stability compared to typical alkyl groups.[19]

The *N*-arylation of indazoles was next evaluated, keeping in mind that a mixture of regioisomers resulting from arylation at N1 and N2 is often obtained with other methods.[18,20] When 1*H*-indazole-6-carbaldehyde 7 was subjected to our conditions, the product 8a generated from the arylation of N1 was predominantly formed (Scheme 5). The structure of the minor regioisomer 8b obtained from the arylation of N2 was established by X-ray crystallography.

Derivatives of tryptophan are important in medicinal chemistry as these species are involved in numerous biological processes and diseases.[21] The post-synthetic modification of peptides containing tryptophan residues has also found applications in chemical biology.[22] To the best of our knowledge, very few methods for the *N*-arylation of tryptophan derivatives have been reported in the literature.[23] Notably, Boc- and Fmoc-protected tryptophan derivatives 9a and 9b were smoothly *N*-arylated using our protocol to selectively provide the *N*-indolyl derivatives 10a, b in good yield (Scheme 6).[24]

Conclusions

In summary, we have developed an efficient and general method for the *N*-arylation of indoles, indazoles, pyrroles, and pyrazoles that proceeds directly using highly functionalized trivalent organobismuth reagents. The transformation is promoted by catalytic amounts of copper acetate and tolerates an exceptional diversity of functional groups on both coupling partners, giving access to highly functionalized azoles. The protocol was also applied to the *N*-arylation of tryptophan derivatives. Application of this methodology to other arylation reactions, including amino-acids and tryptophan-containing peptides, is in progress in our laboratory and the results will be reported in due course.

Acknowledgements

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Notes and references

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ANNEXE F

"COPPER-CATALYZED *N*-ARYLATION OF AZOLES AND DIAZOLES USING HIGHLY FUNCTIONALIZED TRIVALENT ORGANOBISMUTH REAGENTS" SUPPORTING INFORMATION

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Titre : Copper-Catalyzed *N*-Arylation of Azoles and Diazoles Using Highly Functionnalized Trivalent Organobismuth Reagents

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Supporting Information

Copper-Catalyzed *N*-Arylation of Azoles and Diazoles using Highly Functionalized Trivalent Organobismuth Reagents

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Table of content:

P. Petiot, J. Dansereau and A. Gagnon

1. General information

Unless otherwise indicated, all reactions were run under argon in non-flame dried glassware. For reactions performed under oxygen, 99.6% extra dry oxygen was used. Unless otherwise stated, commercial reagents were used without further purification. Grignard reagents were prepared by conventional methods using metallic magnesium or via Knochel's procedure.[1] Triphenylbismuth was prepared according to Barton *et al.*[2] Triarylbismuthanes were prepared according to procedures that we previously reported.[3,4] Anhydrous solvents were obtained using a MBRAUN (model MB-SPS 800) encapsulated solvent purification system. The evolution of reactions was monitored by analytical thin-layer chromatography using silica gel 60 F254 precoated plates. Flash chromatography was performed employing 230-400 mesh silica (Silicycle) using the indicated solvent system according to standard techniques.[5] Melting points were taken on an Electrothermal Mel-TEMP and are uncorrected. Nuclear magnetic resonance spectra (^{1}H, ^{13}C) were recorded on a Bruker Avance-III 300MHz spectrometer. Chemical shifts for ^{1}H-NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qt = quintuplet, dd = doublet of doublet, m = multiplet), coupling constant *J* in Hz and integration. Chemical shifts for ^{13}C spectra are recorded in parts per million from tetramethylsilane using the central peak of deuterochloroform (δ 77.16 ppm) as the internal standard. IR spectra were recorded on a Thermo Scientific Nicolet 6700 PT-IR from thin films and are reported in reciprocal centimeters (cm^{-1}). HRMS were performed at Université du Québec à Montréal (nanoQAM center) on Agilent Technologies, LC 1200 Series / 6210 TOF LCMS analyzer using the electrospray (ESI) mode.

2. Triarylbismuthanes used in the *N*-arylation reaction of azoles and diazoles

The organobismuthanes used in this publication are illustrated in **Figure S1**.

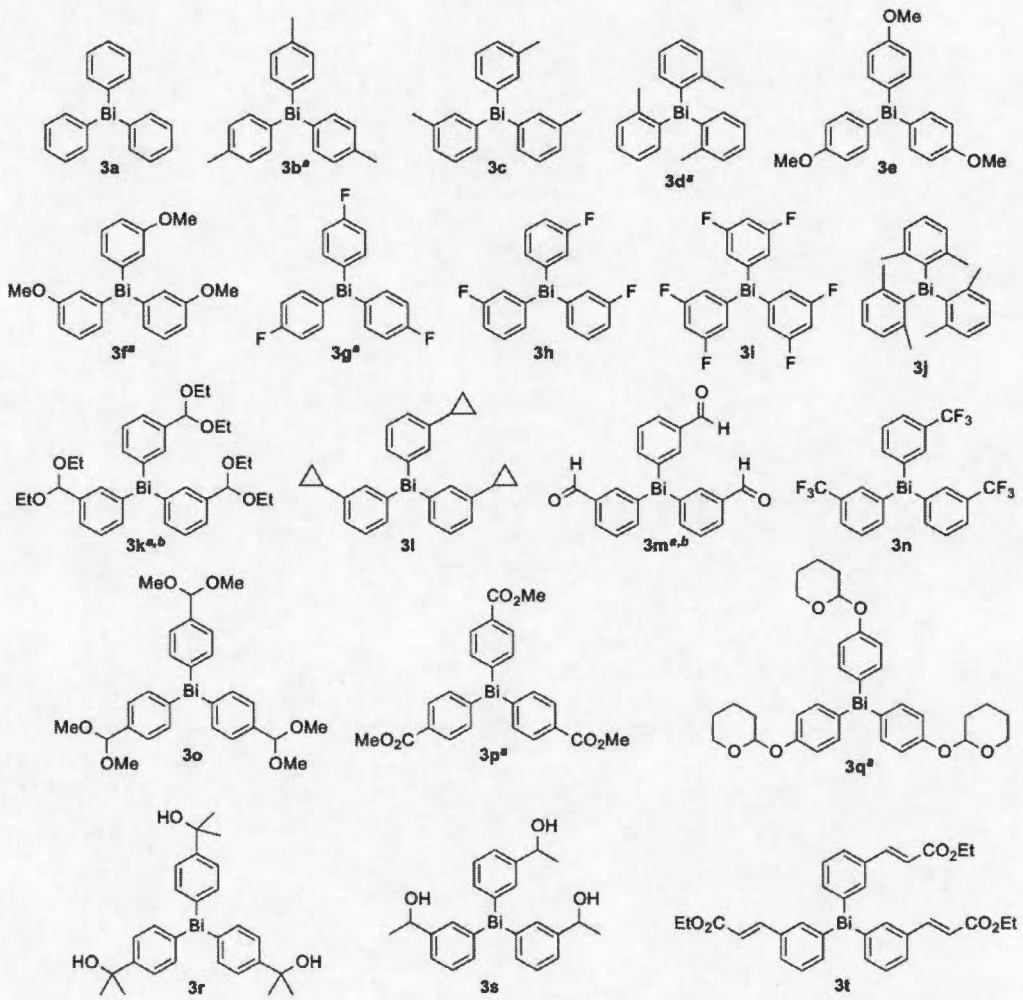


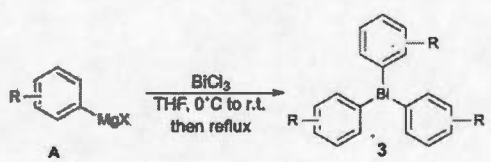
Figure S1. Functionalized organobismuthanes used in this publication. [a] The synthesis of these organobismuthanes has been reported in P. Petiot and A. Gagnon, *Eur. J. Org. Chem.*, 2013, 5282; [b] The synthesis of these organobismuthanes has been reported in C. Crifar, P. Petiot, T. Ahmad and A. Gagnon, *Chem. Eur. J.* **2014**, 2755.

P. Petiot, J. Dansereau and A. Gagnon

3. Synthesis of triarylbismuthanes

Triphenylbismuth was synthesized according to Barton *et al.* (D. H. R. Barton, N. Y. Bhatnagar, J.-P. Finet and W. B. Motherwell, *Tetrahedron*, 1986, **42**, 3111). Triarylbismuthanes **3b**, **3d**, **3f**, **3g**, **3k**, **3m**, **3p** and **3q** were synthesized according to P. Petiot and A. Gagnon (*Eur. J. Org. Chem.*, **2013**, 5282) and C. Crifar, P. Petiot, T. Ahmad and A. Gagnon (*Chem. Eur. J.*, **2014**, 2755). The procedure for the preparation of organobismuthanes **3c**, **3e**, **3h**, **3i**, **3j**, **3l**, **3n**, **3o**, **3r**, **3s**, and **3t** is described below.

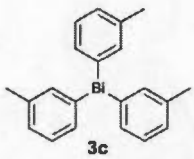
a) General procedure for the synthesis of substituted triarylbismuthanes



In a flask equipped with a magnetic stir bar and a condenser, bismuth chloride (500 mg, 1.6 mmol) was dissolved in anhydrous THF (23 mL) under argon and was cooled to –10°C (ice/acetone bath). The organomagnesium reagent **A** (5.23 mmol) was slowly added dropwise under argon. The reaction mixture was stirred at room temperature for one hour and heated at 65°C for 30 minutes. After cooling to r.t., the solution was diluted with sat. aq. $NaHCO_3$ (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (2 x 100 mL), sat. aq. NaCl (2 x 100 mL), dried over $Na_2S_2O_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using the indicated solvent system to afford the desired triarylbismuthane **3**.

P. Petiot, J. Dansereau and A. Gagnon

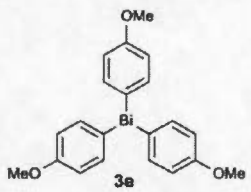
Tris(3-methylphenyl)bismuthine (3c)



3c

The general procedure was followed on a 2.4 mmol scale starting from bismuth chloride and 3-tolylmagnesium bromide. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford tris(3-methylphenyl)bismuthine (**3c**) as a white solid (1.0 g, 87%); m.p. 64-66°C. Spectral data was identical to literature compound[6]: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.31-7.29 (m, 1H), 7.13 (d, J = 7.4 Hz, 1H), 2.31 (s, 3H).

Tris(4-methoxyphenyl)bismuthine (3e)

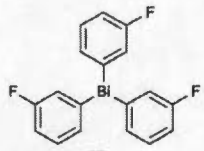


3e

The general procedure was followed on a 4.4 mmol scale starting from bismuth chloride and 4-methoxyphenylmagnesium bromide. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford tris(4-methoxyphenyl)bismuthine (**3e**) as a white solid (1.8 g, 78%): m.p. 70-74°C. Spectral data was identical to literature compound[6]: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.62 (d, J = 8.5 Hz, 2H), 6.92 (d, J = 8.5 Hz, 2H), 3.79 (s, 3H).

P. Petiot, J. Dansereau and A. Gagnon

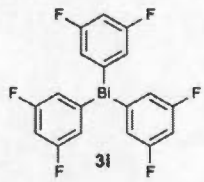
Tris(3-fluorophenyl)bismuthine (3h)



3h

The general procedure was followed on a 2.5 mmol scale starting from bismuth chloride and 3-fluorophenylmagnesium bromide. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford tris(3-fluorophenyl)bismuthine (**3h**) as a white solid (1.0 g, 81%); m.p. 69-73°C. Spectral data was identical to literature compound[7]: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.50-7.39 (m, 3H), 7.06-6.99 (m, 1H).

Tris(3,5-difluorophenyl)bismuthine (3i)

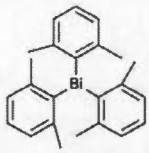


3i

The general procedure was followed on a 2.7 mmol scale starting from bismuth chloride and 3,5-difluorophenylmagnesium bromide. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford tris(3,5-difluorophenyl)bismuthine (**3i**) as a yellow solid (1.1 g, 74%): m.p. 100-104°C; R_f 0.68 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.57-7.52 (m, 2H), 7.10-7.03 (m, 1H); ^{13}C-NMR (75 MHz, CDCl3) δ 167.5 (d, J = 9.8 Hz), 164.2 (d, J = 9.8 Hz), 119.7 (dd, J = 15.9, 6.4 Hz), 104.6 (t, J = 24.8 Hz); IR (neat) 3088, 1582, 1410, 1263, 1116; HRMS (ESI) calcd for $C_{18}H_9BiF_6$: 548.0412, found 593.0395 ($M+HCO_2$).

P. Petiot, J. Dansereau and A. Gagnon

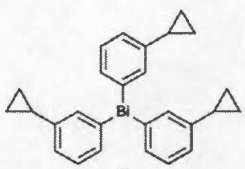
Tris(2,6-dimethylphenyl)bismuthine (3j)



3j

The general procedure was followed on a 2.5 mmol scale starting from bismuth chloride and 2,6-dimethylphenylmagnesium bromide. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford tris(2,6-dimethylphenyl)bismuthine (**3j**) as a white solid (1.1 g, 84%): m.p. 128-130°C; R_f 0.80 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.14-7.10 (m, 3H), 2.34 (s, 6H); ^{13}C-NMR (75 MHz, CDCl3) δ 159.4, 146.0, 128.3, 127.9, 28.1; IR (neat) 3045, 2960, 2918, 1442, 763.

Tris(3-cyclopropylphenyl)bismuthine (3l)

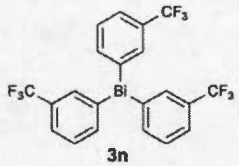


3l

The general procedure was followed on a 0.31 mmol scale starting from bismuth chloride and 3-cyclopropylphenylmagnesium bromide. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford tris(3-cyclopropylphenyl)bismuthine (**3l**) as a colorless oil (151 mg, 87%): R_f 0.71 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.53-7.47 (m, 2H), 7.30-7.25 (m, 2H), 7.01 (d, J = 7.9 Hz, 1H), 1.87-1.81 (m, 1H), 0.95-0.88 (m, 2H), 0.65-0.61 (m, 2H); ^{13}C-NMR (75 MHz, CDCl3) δ 155.1, 145.8, 135.0, 134.8, 130.4, 125.1, 15.6, 9.5; IR (neat) 3078, 3039, 3001, 1589, 1560.

P. Petiot, J. Dansereau and A. Gagnon

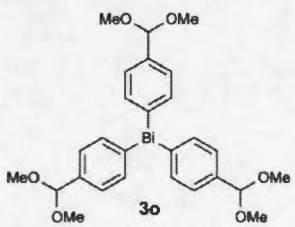
Tris(3-trifluoromethylphenyl)bismuthine (3n)



3n

The general procedure was followed on a 4.4 mmol scale starting from bismuth chloride and 3-trifluoromethylphenylmagnesium bromide. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford tris(3-trifluoromethylphenyl)bismuthine (**3n**) as a yellow oil (2.7 g, 95%): R_f 0.56 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.90 (d, J = 7.3 Hz, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.58-7.53 (m, 1H); ^{13}C-NMR (75 MHz, CDCl3) δ 156.2, 140.8 (d, J = 1.2 Hz), 133.9 (q, J = 3.8 Hz), 132.8 (q, J = 31.8 Hz), 131.2, 125.3 (q, J = 3.8 Hz), 122.5; IR (neat) 3051, 2959, 1592, 1319, 1308, 1114, 1070; HRMS (ESI) calcd for $C_{21}H_{12}BiF_9$: 644.0599, found 689.0592 (M+HCO_2).

Tris(4-(dimethoxymethyl)phenyl)bismuthine (3o)



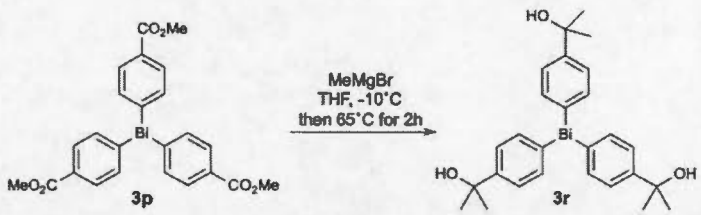
3o

The general procedure was followed on a 3.2 mmol scale starting from bismuth chloride and 4-(dimethoxymethyl)phenylmagnesium bromide. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford tris(4-(dimethoxymethyl)phenyl)-bismuthine (**3o**) as a yellow oil (2.1 g, quant.): R_f 0.32 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 7.8 Hz, 2H), 5.35 (s, 1H), 3.34 (s, 6H); ^{13}C-NMR (75 MHz, CDCl3) δ 155.4,

137.7, 137.5, 128.8, 103.4, 52.9; IR (neat) 2988, 2934, 2903, 2827, 1348, 1207, 1180, 1096, 1048.

b) Procedures for the synthesis of functionalized organobismuthanes by functional group manipulation

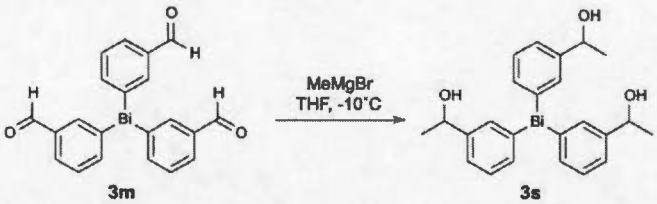
4,4',4''-Bismuthylidyne tris[α,α-dimethylbenzenemethanol] (3r)



A solution of tris(4-carbomethoxyphenyl)bismuthine **3p** (100 mg, 0.2 mmol) in anhydrous THF (5 mL), was cooled to –10°C (acetone/ice bath) and methylmagnesium bromide (0.6 mL, 1.2 mmol, 2M in THF) was added slowly. The reaction mixture was heated at 65°C for 2h, then cooled to r.t., transferred over aq. sat. NH_4Cl (50 mL) and extracted with EtOAc (10 mL). The organic layer was washed with sat. aq. NH_4Cl (10 mL) and sat. aq. NaCl (3 x 10 mL), dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford 4,4',4''-bismuthylidyne tris[α,α-dimethylbenzenemethanol] (**3r**) as a colorless oil (103 mg, 84%): R_f 0.53 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 7.8 Hz, 2H), 7.49 (d, J = 7.7 Hz, 2H), 2.15 (s(br), 1H), 1.56 (s, 6H); ^{13}C-NMR (75 MHz, CDCl3) δ 152.8, 148.7, 137.5, 126.6, 72.6, 31.7; IR (neat) 3375, 3063, 2973, 2925, 2851, 1384, 1169.

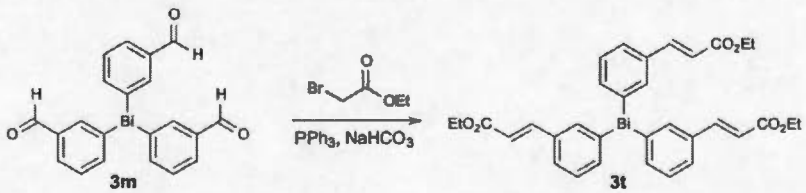
P. Petiot, J. Dansereau and A. Gagnon

3,3',3''-Bismuthylidyne tris[α-methylbenzenemethanol] (3s)



A solution of tris(3-formylphenyl)bismuthine **3m** (400 mg, 0.8 mmol) in anhydrous THF (10 mL), was cooled to –10°C (acetone/ice bath) and methylmagnesium bromide (0.83 mL, 2.5 mmol, 3M in THF) was added slowly. After 10 minutes, the reaction mixture was diluted with aq. sat. NH_4Cl (50 mL) and extracted with EtOAc (20 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (15 mL) and sat. aq. NaCl (3 x 15 mL), dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude material was purified on silica gel (40% EtOAc/hexanes) to afford 3,3',3''-bismuthylidyne tris[α-methylbenzenemethanol] (**3s**) as a white solid (384 mg, 84%): m.p. 78-83°C; R_f 0.32 (80% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.66 (d, J = 7.0 Hz, 1H), 7.40-7.30 (m, 2H), 4.88-4.81 (m, 1H), 1.47-1.43 (m, 3H); ^{13}C-NMR (75 MHz, CDCl3) δ 155.6, 147.6, 136.6, 134.6, 130.4, 125.1, 70.3, 25.1; IR (neat) 3348, 3045, 2972, 2869, 1412, 1264; HRMS (ESI) calcd for $C_{24}H_{27}BiO_3$: 572.1764, found 617.1745 ($M+HCO_2$).

Tris(3-((*E*)-2-propenoic acid ethyl ester)phenyl)bismuthine (3t)

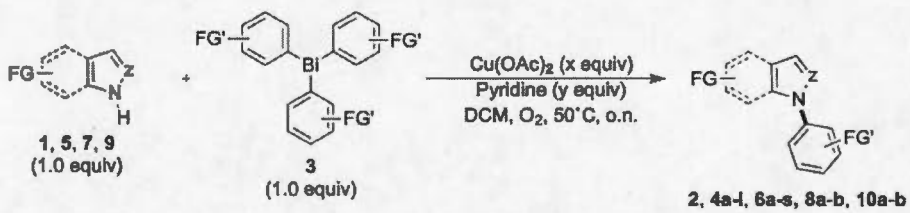


P. Petiot, J. Dansereau and A. Gagnon

A solution of PPh_3 (1.1 g, 4.3 mmol) in sat. aq. $NaHCO_3$ (25 mL) was stirred at r.t., then tris(3-formylphenyl)bismuthine **3m** (500 mg, 0.9 mmol) and ethyl bromoacetate (0.58 mL, 5.2 mmol) were added. The reaction mixture was stirred for 2h, acidified with aq. HCl 1M (5 mL) and then diluted with EtOAc (10 mL). The organic layer was washed with sat. aq. NaCl (3 x 10 mL), dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford tris(3-((*E*)-2-propenoic acid ethyl ester)phenyl)bismuthine (**3t**) as a yellow oil (519 mg, 79%): R_f 0.21 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.73 (d, J = 7.2 Hz, 1H), 7.63 (d, J = 16.1 Hz, 1H), 7.53 (d, J = 7.7 Hz, 1H), 7.44 (t, J = 7.4 Hz, 1H), 6.36 (d, J = 16.0 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl3) δ 166.8, 156.1, 144.5, 139.3, 137.3, 136.6, 131.2, 127.6, 118.7, 60.5, 14.4; IR (neat) 3042, 2980, 2902, 1703, 1633, 1304, 1164; HRMS (ESI) calcd for $C_{33}H_{33}BiO_6$: 734.2081, found 779.2076 ($M+HCO_2$).

4. General procedures for the *N*-arylation of azoles and diazoles

Compound **2**, **4a-i**, **6a-s**, **8a,b** and **10a,b** were prepared according to the following procedures:



Method	Azole (n equiv)	Ar_3Bi (5) (m equiv)	$Cu(OAc)_2$ (x equiv)	Pyridine (y equiv)
A	1.0	1.0	0.1	1.0
B	1.0	1.0	0.1	3.0
C	1.0	1.0	1.0	3.0

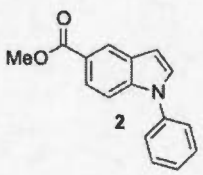
P. Petiot, J. Dansereau and A. Gagnon

Method A: In a sealed tube, triarylbismuthine (1.0 equiv) was added, followed by copper (II) acetate (0.1 equiv) and the azole or diazole (1.0 equiv). The reagents were dissolved in anhydrous dichloromethane (4 mL) and pyridine (1.0 equiv) was added to the mixture. The reaction tube was purged by bubbling dry oxygen in the solution for 30 seconds. The tube was sealed and heated at 50°C overnight. The reaction mixture was cooled to r.t. and transferred in a round bottom flask. Silica gel was added and the mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using EtOAc/hexanes as the eluent to give the corresponding product.

Method B: Idem as method **A** except for pyridine (3.0 equiv instead of 1.0 equiv).

Method C: Idem as method **A** except for copper (II) acetate (1.0 equiv instead of 0.1 equiv) and pyridine (3.0 equiv instead of 1.0 equiv).

1-Phenyl-1*H*-indole-5-carboxylic acid methyl ester (2)

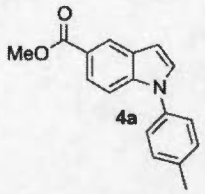


2

Method A was followed on a 0.29 mmol scale starting from methyl 1*H*-indole-5-carboxylate and **3a**. The crude product was purified on silica gel (15% EtOAc/hexanes) to afford **2** as a yellow oil (70 mg, 96%). Spectral data was identical to literature[8]: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.82 (dd, J = 10.2, 1.7 Hz, 1H), 7.44-7.36 (m, 5H), 7.31-7.27 (m, 2H), 6.67 (d, J = 3.2 Hz, 1H), 3.84 (s, 3H).

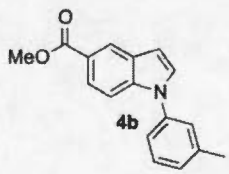
P. Petiot, J. Dansereau and A. Gagnon

1-(4-Methylphenyl)-1*H*-indole-5-carboxylic acid methyl ester (4a)



Method A was followed on a 0.29 mmol scale starting from methyl 1*H*-indole-5-carboxylate and **3b**. The crude product was purified on silica gel (10% EtOAc/hexanes) to afford **4a** as a yellow solid (67 mg, 87%): m.p. 90-92°C; R_f 0.66 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.44 (d, J = 1.5 Hz, 1H), 7.90 (dd, J = 8.8, 1.7 Hz, 1H), 7.50 (d, J = 8.7 Hz, 1H), 7.40-7.32 (m, 5H), 6.75 (d, J = 2.8 Hz, 1H), 3.94 (s, 3H), 2.45 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.1, 138.5, 137.1, 136.8, 130.4, 129.7, 128.8, 124.5, 124.2, 123.7, 122.3, 110.3, 104.6, 52.0, 21.2; IR (neat) 3105, 2938, 2835, 1721, 1709, 1698, 1606, 1523, 1519, 1514, 1446, 1434, 1335, 1311, 1270, 1228, 1197; HRMS (ESI) calcd for $C_{17}H_{15}NO_2$: 265.1103, found 266.1170 (M+H).

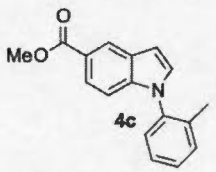
1-(3-Methylphenyl)-1*H*-indole-5-carboxylic acid methyl ester (4b)



Method A was followed on a 0.29 mmol scale starting from methyl 1*H*-indole-5-carboxylate and **3c**. The crude product was purified on silica gel (10% EtOAc/hexanes) to afford **4b** as a yellow oil (67 mg, 87%): R_f 0.52 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.35 (d, J = 1.5 Hz, 1H), 7.82 (dd, J = 8.8, 1.6 Hz, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.33-7.26 (m, 2H), 7.19-7.17 (m, 2H), 7.10 (d, J = 7.6 Hz, 1H), 6.65 (d, J = 3.3 Hz, 1H), 3.84 (s, 3H), 2.35 (s, 3H); ^{13}C-NMR

(75 MHz, $CDCl_3$) δ 168.1, 139.9, 139.2, 138.4, 129.6, 128.9, 127.9, 125.2, 124.2, 123.7, 122.4, 121.7, 110.3, 104.7, 52.0, 21.5; IR (neat) 3105, 2946, 2835, 1709, 1693, 1605, 1445, 1432, 1334, 1270, 1230, 1191; HRMS (ESI) calcd for $C_{17}H_{15}NO_2$: 265.1103, found 266.1177 (M+H).

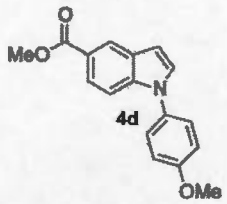
1-(2-Methylphenyl)-1*H*-indole-5-carboxylic acid methyl ester (4c)



Method A was followed on a 0.29 mmol scale starting from methyl 1*H*-indole-5-carboxylate and **3d**. The crude product was purified on silica gel (10% EtOAc/hexanes) to afford **4c** as a yellow oil (19 mg, 24%): R_f 0.52 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.38 (d, J = 1.5 Hz, 1H), 7.78 (dd, J = 8.7, 1.6 Hz, 1H), 7.30-7.21 (m, 4H), 7.12 (d, J = 3.2 Hz, 1H), 6.93 (d, J = 8.7 Hz, 1H), 6.66 (d, J = 2.8 Hz, 1H), 3.84 (s, 3H), 1.94 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.2, 139.5, 137.8, 135.9, 131.4, 130.2, 128.8, 128.1, 127.9, 127.1, 124.1, 123.6, 122.1, 110.3, 104.0, 52.0, 17.6; IR (neat) 3109, 3027, 2950, 2852, 1720, 1712, 1612, 1513, 1501, 1461, 1445, 1434, 1335, 1300, 1269, 1231, 1196; HRMS (ESI) calcd for $C_{17}H_{15}NO_2$: 265.1103, found 266.1170 (M+H). Compound **3c** was also obtained (59 mg, 78%) following method C on a 0.285 mmole scale starting from methyl 1*H*-indole-5-carboxylate.

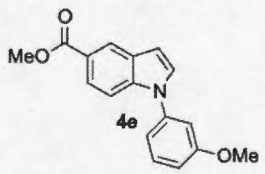
P. Petiot, J. Dansereau and A. Gagnon

1-(4-Methoxyphenyl)-1*H*-indole-5-carboxylic acid methyl ester (4d)



Method A was followed on a 0.28 mmol scale starting from methyl 1*H*-indole-5-carboxylate and **3e**. The crude product was purified on silica gel (15% EtOAc/hexanes) to afford **4d** as a colorless oil (45 mg, 57%): R_f 0.39 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.45 (d, J = 1.5 Hz, 1H), 7.91 (dd, J = 8.7, 1.7 Hz, 1H), 7.45-7.26 (m, 4H), 7.06-7.03 (m, 2H), 6.74 (dd, J = 3.3, 0.7 Hz, 1H), 3.94 (s, 3H), 3.88 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.1, 158.7, 138.8, 132.2, 129.8, 128.5, 126.1, 124.1, 123.6, 122.2, 114.9, 110.1, 104.3, 55.6, 51.9; IR (neat) 3106, 2998, 2949, 2837, 1707, 1611, 1513, 1434, 1298.

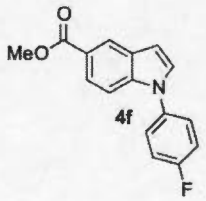
1-(3-Methoxyphenyl)-1*H*-indole-5-carboxylic acid methyl ester (4e)



Method A was followed on a 0.29 mmol scale starting from methyl 1*H*-indole-5-carboxylate and **3f**. The crude product was purified on silica gel (15% EtOAc/hexanes) to afford **4e** as a yellow oil (40 mg, 49%): R_f 0.47 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.44 (d, J = 1.5 Hz, 1H), 7.92 (dd, J = 8.9, 1.7 Hz, 1H), 7.57 (d, J = 8.7 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.41-7.39 (m, 1H), 7.08 (dd, J = 8.7, 2.0 Hz, 1H), 7.04 (t, J = 2.3 Hz, 1H), 6.94 (dd, J = 9.1, 1.0 Hz, 1H), 6.77 (dd, J = 3.3, 0.8 Hz, 1H), 3.95 (s, 3H), 3.87 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ

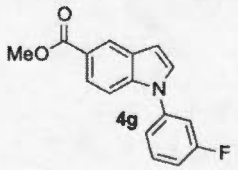
168.0, 160.7, 140.4, 138.3, 130.5, 129.5, 128.9, 124.1, 123.8, 122.5, 116.7, 112.5, 110.5, 110.3, 104.9, 55.6, 51.9; IR (neat) 2998, 2948, 2836, 1708, 1602, 1592, 1493, 1432, 1275; HRMS (ESI) calcd for $C_{17}H_{15}NO_3$: 281.1052, found 282.1128 (M+H).

1-(4-Fluorophenyl)-1*H*-indole-5-carboxylic acid methyl ester (4f)



Method A was followed on a 0.29 mmol scale starting from methyl 1*H*-indole-5-carboxylate and **3g**. The crude product was purified on silica gel (10% EtOAc/hexanes) to afford **4f** as a yellow solid (53 mg, 68%). Spectral data was identical to literature[8]: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.35 (d, J = 1.8 Hz, 1H), 7.82 (dd, J = 8.8, 1.6 Hz, 1H), 7.36-7.31 (m, 3H), 7.22 (d, J = 3.3 Hz, 1H), 7.15-7.09 (m, 2H), 6.66 (d, J = 3.2 Hz, 1H), 3.84 (s, 3H).

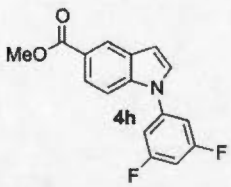
1-(3-Fluorophenyl)-1*H*-indole-5-carboxylic acid methyl ester (4g)



Method A was followed on a 0.29 mmol scale starting from methyl 1*H*-indole-5-carboxylate and **3h**. The crude product was purified on silica gel (10% EtOAc/hexanes) to afford **4g** as a yellow solid (54 mg, 69%): m.p. 95-100°C; R_f 0.41 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.26 (d, J = 1.6 Hz, 1H), 7.76 (dd, J = 8.7, 1.7 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 7.35-7.27 (m,

1H), 7.18 (d, J = 3.3 Hz, 1H), 7.12 (d, J = 8.1 Hz, 2H), 7.09 (td, J = 11.6, 1.5 Hz, 1H), 6.90 (dt, J = 8.5, 2.6 Hz, 1H), 6.59 (d, J = 3.3 Hz, 1H), 3.76 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.9, 164.9, 161.6, 140.8, 140.6, 138.1, 131.1, 131.0, 129.1, 129.0, 124.2, 124.0, 122.8, 120.0, 119.9, 114.1, 113.8, 111.9, 111.6, 110.1, 105.5, 52.0; IR (neat) 3072, 2955, 1714, 1607, 1301, 1283, 1192; HRMS (ESI) calcd for $C_{16}H_{12}FNO_2$: 269.0852, found 270.0933 (M+H).

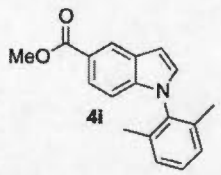
1-(3,5-Difluorophenyl)-1*H*-indole-5-carboxylic acid methyl ester (4h)



Method A was followed on a 0.29 mmol scale starting from methyl 1*H*-indole-5-carboxylate and **3i**. The crude product was purified on silica gel (10% EtOAc/hexanes) to afford **4h** as a yellow solid (43 mg, 52%): m.p. 170-174°C; R_f 0.52 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.44 (d, J = 1.7 Hz, 1H), 7.97 (dd, J = 8.8, 1.7 Hz, 1H), 7.59 (d, J = 8.7 Hz, 1H), 7.36 (d, J = 3.4 Hz, 1H), 7.09-7.06 (m, 2H), 6.88-6.79 (m, 2H), 3.96 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.7, 165.3, 165.1, 162.0, 161.8, 141.4, 141.2, 137.8, 129.2, 128.7, 124.4, 124.3, 123.2, 110.0, 107.7, 107.6, 107.5, 107.3, 106.1, 102.8, 102.4, 102.1, 52.1; IR (neat) 3099, 2959, 2922, 1708, 1626, 1598, 1283, 1193, 1116; HRMS (ESI) calcd for $C_{16}H_{11}F_2NO_2$: 287.0758, found 288.0834 (M+H).

P. Petiot, J. Dansereau and A. Gagnon

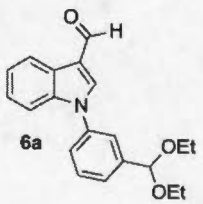
1-(2,6-Dimethylphenyl)-1*H*-indole-5-carboxylic acid methyl ester (4i)



4i

Method A was followed on a 0.29 mmol scale starting from methyl 1*H*-indole-5-carboxylate and **3j**. The crude product was purified on silica gel (5% EtOAc/hexanes) to afford **4i** as a yellow oil (15 mg, 19%): R_f 0.53 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.47 (d, J = 1.6 Hz, 1H), 7.85 (dd, J = 8.5, 1.7 Hz, 1H), 7.29-7.04 (m, 4H), 6.88 (d, J = 8.6 Hz, 1H), 6.78 (d, J = 3.3 Hz, 1H), 3.92 (s, 3H), 1.90 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.2, 138.8, 137.1, 136.5, 129.5, 128.8, 128.6, 128.5, 127.7, 124.0, 123.5, 122.0, 109.8, 104.0, 51.9, 17.4; IR (neat) 2948, 2922, 1708, 1611, 1446, 1434, 1295, 1269; HRMS (ESI) calcd for $C_{18}H_{17}NO_2$: 279.1259, found 280.1347 (M+H).

1-((3-Diethoxymethyl)phenyl)-1*H*-indole-3-carboxaldehyde (6a)

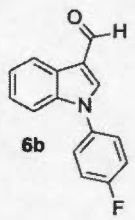


6a

Method A was followed on a 0.34 mmol scale starting from 1*H*-indole-3-carbaldehyde and **3k**. The crude product was purified on silica gel (20% EtOAc/hexanes) to afford **6a** as a yellow oil (101 mg, 92%): R_f 0.18 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.10 (s, 1H), 8.38 (d, J = 8.2 Hz, 1H), 7.93 (s, 1H), 7.67 (s, 1H), 7.59-7.54 (m, 2H), 7.49-7.46 (m, 2H), 7.38-7.30 (m, 2H), 5.60 (s, 1H), 3.74-3.55 (m, 4H), 1.28 (t, J = 7.0 Hz, 6H); ^{13}C-NMR (75 MHz,

$CDCl_3$) δ 185.0, 141.8, 138.2, 137.5, 129.8, 126.6, 125.6, 124.7, 124.6, 123.5, 123.1, 122.3, 119.8, 111.1, 100.7, 61.4, 15.3; IR (neat) 3117, 3052, 2966, 2868, 2807, 2762, 2725, 1665, 1660, 1605, 1530, 1493, 1480, 1461, 1309; HRMS (ESI) calcd for $C_{20}H_{21}NO_3$: 323.1521, found 324.1584 (M+H).

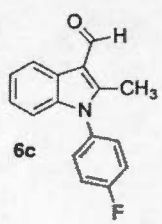
1-(4-Fluorophenyl)-1*H*-indole-3-carboxaldehyde (6b)



6b

Method A was followed on a 0.34 mmol scale starting from 1*H*-indole-3-carbaldehyde and **3g**. The crude product was purified on silica gel (20% EtOAc/hexanes) to afford **6b** as a white solid (43 mg, 52%): m.p. 141-143°C. Spectral data was identical to literature[9]: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.00 (s, 1H), 8.29 (dd, J = 5.6, 2.0 Hz, 1H), 7.77 (s, 1H), 7.43-7.38 (m, 2H), 7.33-7.16 (m, 5H); HRMS (ESI) calcd for $C_{15}H_{10}FNO$: 239.0746, found 240.0813 (M+H).

1-(4-Fluorophenyl)-2-methyl-1*H*-indole-3-carboxaldehyde (6c)

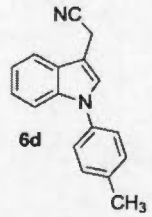


6c

Method A was followed on a 0.31 mmol scale starting from 2-methyl-1*H*-indole-3-carbaldehyde and **3g**. The crude product was purified on silica gel (20% EtOAc/hexanes) to afford **6c** as a

white solid (60 mg, 76%): m.p. 174-176°C; R_f 0.21 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.15 (s, 1H), 8.21 (d, J = 7.8 Hz, 1H), 7.27-7.17 (m, 5H), 7.12 (t, J = 7.3 Hz, 1H), 6.90 (d, J = 8.1 Hz, 1H), 2.44 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 184.8, 164.5, 161.2, 147.8, 138.3, 132.0, 130.0, 129.9, 125.7, 123.7, 123.4, 121.0, 117.3, 117.0, 115.3, 110.4, 11.4; IR (neat) 3068, 2929, 2827, 1642, 1511, 1503, 1480, 1461, 1426, 1225, 1218; HRMS (ESI) calcd for $C_{16}H_{12}FNO$: 253.0903, found 254.0981 (M+H).

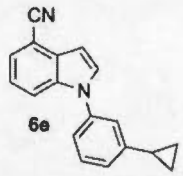
1-(4-Methylphenyl)-1*H*-indole3-acetonitrile (6d)



Method C was followed on a 0.32 mmol scale starting from 1*H*-indole-3-ylacetonitrile and **3b**. The crude product was purified on silica gel (15% EtOAc/hexanes) to afford **6d** as a red oil (69 mg, 88%): R_f 0.37 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.51 (d, J = 7.1 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.24-7.08 (m, 7H), 3.74 (s, 2H), 2.31 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 136.9, 136.7, 136.5, 130.3, 127.2, 126.7, 124.4, 123.2, 120.7, 118.5, 118.1, 111.1, 105.4, 21.1, 14.4; IR (neat) 3040, 2917, 2856, 2251, 1646, 1611, 1518, 1514, 1461, 1454; HRMS (ESI) calcd for $C_{17}H_{14}N_2$: 246.1157, found 247.1223 (M+H).

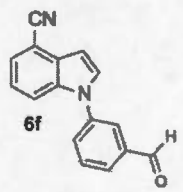
P. Petiot, J. Dansereau and A. Gagnon

1-(3-Cyclopropylphenyl)-1*H*-indole-4-carbonitrile (6e)



Method C was followed on a 0.27 mmol scale starting from 4-cyanoindole and **3l**. The crude product was purified on silica gel (15% EtOAc/hexanes) to afford **6e** as a yellow oil (61 mg, 88%): R_f 0.53 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 8.4 Hz, 1H), 7.43-7.29 (m, 3H), 7.16-7.11 (m, 2H), 7.05-7.01 (m, 2H), 6.78 (d, J = 3.1 Hz, 1H), 1.93-1.84 (m, 1H), 0.99-0.93 (m, 2H), 0.70-0.64 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 146.6, 138.8, 135.9, 130.8, 130.5, 129.8, 125.7, 124.9, 122.2, 122.0, 121.8, 118.7, 115.5, 103.6, 102.2, 15.6, 9.8; IR (neat) 3077, 3007, 2917, 2831, 2227, 1587, 1511, 1503, 1494, 1462, 1444, 1428, 1330; HRMS (ESI) calcd for $C_{18}H_{14}N_2$: 258.1157, found 259.1225 (M+H).

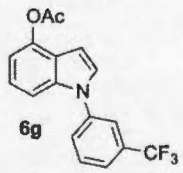
1-(3-Formylphenyl)-1*H*-indole-4-carbonitrile (6f)



Method A was followed on a 0.35 mmol scale starting from 4-cyanoindole and **3m**. The crude product was purified on silica gel (10% EtOAc/hexanes) to afford **6f** as a white solid (53 mg, 62%): m.p. 124-127°C; R_f 0.18 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.90 (d, J = 1.2 Hz, 1H), 7.85 (dt, J = 4.6, 1.5 Hz, 1H), 7.68-7.62 (m, 3H), 7.46-7.44 (m, 2H), 7.22-7.17 (m, 1H), 6.84 (dd, J = 3.3, 0.5 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 191.1,

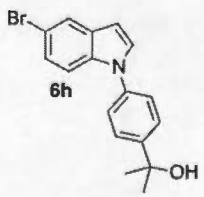
139.8, 138.1, 135.6, 130.9, 130.8, 130.4, 130.2, 129.1, 126.2, 124.6, 122.6, 118.4, 115.1, 104.0, 103.3; IR (neat) 3129, 3105, 2921, 2831, 2733, 2218, 1702, 1692, 1586, 1514, 1492, 1484, 1461, 1432, 1328, 1301, 1184, 1144; HRMS (ESI) calcd for $C_{16}H_{10}N_2O$: 246.0793, found 247.0860 (M+H).

1-(3-Trifluoromethylphenyl)-1*H*-indol-4-ol-4-acetate (6g)



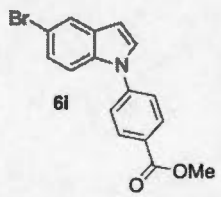
Method C was followed on a 0.29 mmol scale starting from 1*H*-indol-4-yl acetate and **3n**. The crude product was purified on silica gel (20% EtOAc/hexanes) to afford **6g** as a black solid (40 mg, 43%): m.p. 74-76°C; R_f 0.33 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.62-7.54 (m, 3H), 7.31 (d, *J* = 8.3 Hz, 1H), 7.23 (d, *J* = 3.3 Hz, 1H), 7.17-7.12 (m, 1H), 6.86 (d, *J* = 7.7 Hz, 1H), 6.53 (d, *J* = 3.2 Hz, 1H), 2.34 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.4, 144.0, 140.2, 137.6, 132.7, 132.3, 130.5, 128.0, 127.7, 123.6, 123.3, 122.9, 121.4, 113.2, 108.4, 101.4, 21.2; IR (neat) 2913, 1765, 1618, 1593, 1493, 1462, 1335, 1323, 1197, 1125; HRMS (ESI) calcd for $C_{17}H_{12}F_3NO_2$: 319.0820, found 320.0891 (M+H).

4-(5-Bromo-1*H*-indol-1-yl)-α,α-dimethylbenzenemethanol (6h)



Method C was followed on a 0.063 mmol scale starting from 5-bromoindole and **3r**. The crude product was purified on silica gel (25% EtOAc/hexanes) to afford **6h** as a pink wax (11 mg, 53%): R_f 0.27 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 1.7 Hz, 1H), 7.57 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 7.25-7.18 (m, 3H), 6.53 (d, J = 3.1 Hz, 1H), 1.73 (s (br), 1H), 1.58 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 148.0, 138.0, 134.8, 131.1, 129.2, 126.0, 125.3, 124.2, 123.7, 113.6, 112.1, 103.1, 72.5, 32.0; IR (neat) 3379, 2974, 2921, 2844, 1610, 1519, 1514, 1461, 1453; HRMS (ESI) calcd for $C_{17}H_{16}BrNO$: 329.0415, found 312.0373 (M+H)-[H_2O] (^{79}Br), 314.0352 (M+H)-[H_2O] (^{81}Br).

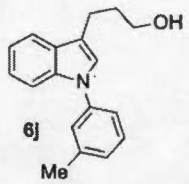
4-(5-Bromo-1*H*-indol-1-yl)benzoic acid methyl ester (6i)



Method C was followed on a 0.24 mmol scale starting from 5-bromoindole and **3p**. The crude product was purified on silica gel (15% EtOAc/hexanes) to afford **6i** as a pink solid (53 mg, 67%): m.p. 94-98°C; R_f 0.52 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.20 (d, J = 8.6 Hz, 2H), 7.82 (d, J = 2.0 Hz, 1H), 7.56 (d, J = 8.6 Hz, 2H), 7.48 (d, J = 8.8 Hz, 1H), 7.37 (d, J = 3.3 Hz, 1H), 7.33 (dd, J = 8.8, 1.7 Hz, 1H), 6.66 (d, J = 3.2 Hz, 1H), 3.97 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.3, 143.3, 134.3, 131.5, 131.4, 128.7, 128.2, 125.8, 124.0, 123.4, 114.2, 112.1, 104.4, 52.4; IR (neat) 2946, 2840, 1720, 1712, 1666, 1605, 1514, 1450, 1434, 1276; HRMS (ESI) calcd for $C_{16}H_{12}BrNO_2$: 329.0051, found 330.0117 (M+H) (^{79}Br), 332.0100 (M+H) (^{81}Br).

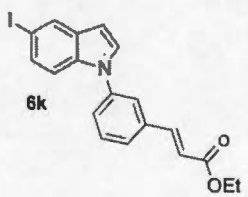
P. Petiot, J. Dansereau and A. Gagnon

1-(3-Methylphenyl)-1*H*-Indole-3-propanol (6j)



Method C was followed on a 0.29 mmol scale starting from 3-(3-hydroxypropyl)-1*H*-indole and **3c**. The crude product was purified on silica gel (20% EtOAc/hexanes) to afford **6j** as a yellow oil (40 mg, 52%): R_f 0.21 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.69 (d, J = 7.2 Hz, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.43-7.38 (m, 1H), 7.32-7.15 (m, 5H), 3.79 (t, J = 6.4 Hz, 2H), 2.94 (t, J = 7.5 Hz, 2H), 2.46 (s, 3H), 2.06 (qt, J = 6.4 Hz, 2H), 1.49 (s(br), 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 139.9, 139.7, 136.1, 129.4, 128.9, 126.9, 125.3, 124.8, 122.4, 121.2, 119.8, 119.3, 116.9, 110.7, 62.7, 32.9, 21.5, 21.3; IR (neat) 3339 (br), 3047, 2922, 2863, 1605, 1588, 1493, 1477, 1458; HRMS (ESI) calcd for $C_{18}H_{19}NO$: 265.1467, found 266.1544 (M+H), 248.1408 [(M+H)-H_2O].

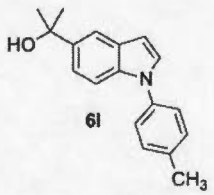
(*E*)-3-(5-Iodo-1*H*-indol-1-yl)phenyl-2-propenoic acid ethyl ester (6k)



Method C was followed on a 0.14 mmol scale starting from 5-iodoindole and **3t**. The crude product was purified on silica gel (10% EtOAc/hexanes) to afford **6k** as a pink oil (38 mg, 65%): R_f 0.52 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 1.7 Hz, 1H), 7.78 (d, J = 16.1 Hz, 1H), 7.66 (s, 1H), 7.61-7.52 (m, 4H), 7.37-7.32 (m, 2H), 6.68 (d, J = 3.4 Hz, 1H), 6.56

(d, J = 16.1 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.6, 143.3, 139.9, 136.3, 134.9, 131.9, 130.9, 130.4, 130.1, 128.5, 126.4, 125.8, 123.5, 119.9, 112.3, 103.3, 84.1, 60.8, 14.4; IR (neat) 3056, 2978, 1705, 1638, 1582, 1512, 1487, 1456, 1176; HRMS (ESI) calcd for $C_{19}H_{16}INO_2$: 417.0226, found 418.0296 (M+H).

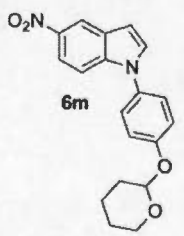
α,α-Dimethyl-1-(4-methylphenyl)-1*H*-indole-5-methanol (6l)



6l

Method A was followed on a 0.28 mmol scale starting from α,α-dimethyl-1*H*-indole-5-methanol and **3b**. The crude product was purified on silica gel (20% EtOAc/hexanes) to afford **6l** as a yellow oil (44 mg, 59%): R_f 0.38 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 1.8 Hz, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.43-7.32 (m, 6H), 6.68 (d, J = 3.3 Hz, 1H), 2.46 (s, 3H), 1.70 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 141.3, 137.4, 136.3, 134.9, 130.2, 129.0, 128.5, 124.2, 119.6, 116.5, 110.3, 103.5, 72.9, 32.2, 21.1; IR (neat) 3405, 2971, 2923, 1517, 1474, 1334; HRMS (ESI) calcd for $C_{18}H_{19}NO$: 265.1467, found 248.1431 [(M+H)-H_2O].

1-[4-(Tetrahydro-2*H*-pyran-2-yl)oxy]phenyl-5-nitro-1*H*-indole (6m)

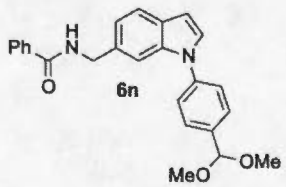


6m

P. Petiot, J. Dansereau and A. Gagnon

Method A was followed on a 0.31 mmol scale starting from 5-nitroindole and **3q**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **6m** as a yellow solid (77 mg, 74%): m.p. 99-104°C; R_f 0.36 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$); δ 8.62 (d, J = 2.2 Hz, 1H), 8.09 (dd, J = 9.1, 2.2 Hz, 1H), 7.46-7.36 (m, 4H), 7.26-7.21 (m, 2H), 6.81 (d, J = 3.3 Hz, 1H), 5.50 (t, J = 3.3 Hz, 1H), 3.93 (dt, J = 9.1, 3.2 Hz, 1H), 3.70-3.64 (m, 1H), 2.12-1.96 (m, 1H), 1.94-1.90 (m, 2H), 1.79-1.62 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 156.6, 142.0, 139.1, 132.2, 131.6, 128.2, 126.1, 118.3, 117.8, 117.6, 110.5, 105.2, 96.6, 62.2, 30.3, 25.2, 18.7; IR (neat) IR 2917, 2852, 1610, 1514, 1468, 1453, 1344, 1329, 1202, 1123, 1069, 966, 920; HRMS (ESI) calcd for $C_{19}H_{18}N_2O_4$: 338.1267, found 339.1333 (M+H).

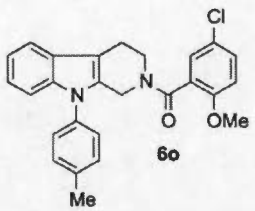
_N_-[4-(dimethoxymethyl)-1_H_-indol-6-yl]methyl benzamide (6n)



Method C was followed on a 0.20 mmol scale starting from 1*H*-indol-6-yl]methyl benzamide and **3o**. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford **6n** as a pink oil (65 mg, 81%): R_f 0.10 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.77-7.74 (m, 2H), 7.68-7.60 (m, 3H), 7.55 (s, 1H), 7.51-7.48 (m, 3H), 7.42-7.40 (m, 2H), 7.35 (d, J = 3.4 Hz, 1H), 7.19 (dd, J = 8.2, 1.5 Hz, 1H), 6.68 (d, J = 3.2 Hz, 1H), 6.38 (s(br), 1H), 5.46 (s, 1H), 4.72 (d, J = 5.4 Hz, 2H), 3.39 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.2, 139.6, 136.7, 135.9, 134.6, 132.4, 131.5, 128.9, 128.6, 128.5, 128.2, 127.0, 124.1, 121.6, 120.9, 110.3, 103.7, 102.7, 52.9, 45.0, IR (neat) 3317, 2933, 2829, 1639, 1518, 1450, 1340, 1098; HRMS (ESI) calcd for $C_{25}H_{24}N_2O_3$: 400.1787, found 423.1695 (M+Na).

P. Petiot, J. Dansereau and A. Gagnon

1-(5-Chloro-2-methoxyphenyl)-1-(2-(4-methylphenyl)-1,3,4,9-tetrahydro-2*H*-pyrido[3,4-*b*]indol-2-yl)methanone (6o)

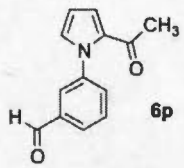


6o

Method C was followed on a 0.15 mmol scale starting from (5-chloro-2-methoxyphenyl)-(1,3,4,9-tetrahydro-2*H*-pyrido[3,4-*b*]indol-2-yl)methanone and **3b**. The crude product was purified on silica gel (10% EtOAc/hexanes) to afford **6o** as a yellow oil (28 mg, 43%): R_f 0.16 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.53-7.50 (m, 1H), 7.35-7.29 (m, 5H), 7.27-7.23 (m, 2H), 7.22-7.14 (m, 2H), 6.89 (d, J = 8.9 Hz, 1H), 4.82 (s, 2H), 3.83 (s, 3H), 3.65-3.60 (m, 2H), 2.88-2.82 (m, 2H), 2.46 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.2, 154.2, 137.8, 134.5, 130.4, 130.3, 130.2, 127.8, 127.5, 126.8, 126.6, 126.4, 126.1, 122.0, 120.0, 117.9, 112.4, 110.3, 108.6, 56.0, 45.2, 40.4, 22.1, 21.2; IR (neat) 2925, 2840, 1709, 1659, 1650, 1641, 1632, 1605, 1514, 1493, 1484, 1461, 1440, 1432, 1221; HRMS (ESI) calcd for $C_{26}H_{23}ClN_2O_2$: 430.1448, found 431.1515 (M+H).

P. Petiot, J. Dansereau and A. Gagnon

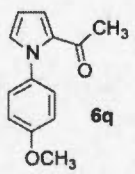
2-Acetyl-N-(3-benzaldehyde)-pyrrole (6p)



6p

Method B was followed on a 0.46 mmol scale starting from 2-acetyl-1*H*-pyrrole and **3m**. The crude product was purified on silica gel (10% EtOAc/hexanes) to afford **6p** as a beige solid (93 mg, 95%): m.p. 85-87°C; R_f 0.16 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.80 (d, J = 7.1 Hz, 1H), 7.69 (s, 1H), 7.52-7.43 (m, 2H), 7.05 (d, J = 2.7 Hz, 1H), 6.89 (s, 1H), 6.25 (t, J = 2.6 Hz, 1H), 2.36 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 191.4, 187.4, 141.8, 137.0, 132.3, 131.6, 131.2, 129.4, 129.1, 126.8, 121.1, 109.9, 27.2; IR (neat) 3117, 3060, 2921, 2827, 2729, 1702, 1692, 1665, 1659, 1650, 1643, 1590, 1461, 1453, 1408; HRMS (ESI) calcd for $C_{13}H_{11}NO_2$: 213.0790, found 214.0859 (M+H).

2-Acetyl-*N*-(4-methoxyphenyl)pyrrole (6q)

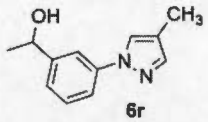


6q

Method A was followed on a 0.46 mmol scale starting from 2-acetyl-1*H*-pyrrole and **3e**. The crude product was purified on silica gel (10% EtOAc/hexanes) to afford **6q** as a colorless oil (78 mg, 79%): m.p. 79-82°C. Spectral data was identical to literature[10]: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.08 (d, J = 8.7 Hz, 2H), 6.97 (d, J = 3.8 Hz, 1H), 6.83-6.80 (m, 3H), 6.17 (t, J = 3.3 Hz, 1H), 3.74 (s, 3H), 2.31 (s, 3H); HRMS (ESI) calcd for $C_{13}H_{13}NO_2$: 215.0946, found 216.1017 (M+H).

P. Petiot, J. Dansereau and A. Gagnon

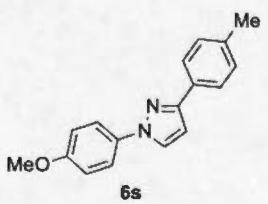
1-[3-(1-Hydroxyethyl)phenyl]-4-methyl-1*H*-pyrazole (6r)



6r

Method C was followed on a 0.50 mmol scale starting from 4-methyl-1*H*-pyrazole and **3s**. The crude product was purified on silica gel (20% EtOAc/hexanes) to afford **6r** as a colorless oil (70 mg, 69%): R_f 0.12 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.63-7.62 (m, 1H), 7.49-7.45 (m, 2H), 7.34 (t, J = 7.7 Hz, 1H), 7.22-7.19 (m, 1H), 4.88 (q, J = 6.5 Hz, 1H), 3.02 (s(br), 1H), 2.14 (s, 3H), 1.48 (d, J = 6.4 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 147.7, 141.8, 140.2, 129.4, 125.6, 123.1, 118.2, 117.6, 115.9, 69.9, 25.3, 8.9; IR (neat) 3354, 2971, 2927, 1610, 1593, 1492, 1455, 1390; HRMS (ESI) calcd for $C_{12}H_{14}N_2O$: 202.1106, found [(M+H)-H_2O)] 185.1059, 203.1175 (M+H).

1-(4-Methoxyphenyl)-3-(4-methylphenyl)-1*H*-pyrazole (6s)

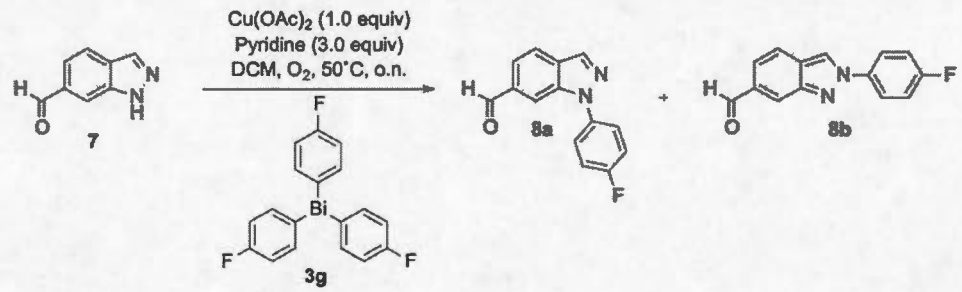


6s

Method C was followed on a 0.32 mmol scale starting from 3-(4-methylphenyl)-1*H*-pyrazole and **3e**. The crude product was purified on silica gel (10% EtOAc/hexanes) to afford **6s** as a white solid (59 mg, 70%): m.p. 140-143°C; R_f 0.50 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.72-7.69 (m, 3H), 7.55 (d, J = 8.7 Hz, 2H), 7.13 (d, J = 7.4 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 6.60 (s, 1H), 3.73 (s, 3H), 2.29 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.2, 152.7, 137.7, 134.2, 130.6, 129.4, 128.0, 125.8, 120.8, 114.6, 104.5, 55.7, 21.4; IR (neat) 3138, 2999,

2909, 2835, 1605, 1524, 1519, 1514, 1503, 1462, 1453, 1434, 1257; HRMS (ESI) calcd for $C_{17}H_{16}N_2O$: 264.1263, found 265.1328 (M+H). The position of the transferred aryl group was determined by nOesy NMR studies.

1-(4-Fluorophenyl)-1*H*-indazole-6-carboxaldehyde (8a) and 2-(4-fluorophenyl)-2*H*-indazole-6-carboxaldehyde (8b)

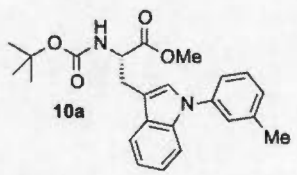


Method C was followed on a 0.34 mmol scale starting from 1*H*-indazole-6-carboxaldehyde **7** and **3g**. The crude product was purified on silica gel (15% EtOAc/hexanes) to afford **8a** as a yellow solid (41 mg, 50%) and **8b** as an orange solid (6.8 mg, 8%).

Compound **8a**: m.p. 143-145°C; R_f 0.50 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.07 (s, 1H), 8.22 (s, 1H), 8.10 (s, 1H), 7.87 (d, J = 8.3 Hz, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.66-7.62 (m, 2H), 7.23 (d, J = 8.5 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 192.8, 164.0, 160.7, 139.4, 136.4, 136.2, 136.1, 129.4, 125.7, 125.6, 122.9, 122.1, 117.6, 117.3, 114.2; IR (neat) 2969, 2815, 2725, 1703, 1698, 1692, 1681, 1605, 1519, 1514, 1503, 1493, 1461, 1450, 1434, 1279; HRMS (ESI) calcd for $C_{14}H_9FN_2O$: 240.0699, found 241.0766 (M+H).

Compound **8b**: m.p. 179-183°C; R_f 0.42 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.10 (s, 1H), 8.43 (s, 1H), 8.30 (s, 1H), 7.93-7.89 (m, 2H), 7.81 (d, J = 8.8 Hz, 1H), 7.66 (d, J = 8.7 Hz, 1H), 7.29-7.24 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 192.4, 149.1, 135.9, 126.3, 125.7, 123.2, 123.1, 121.6, 121.3, 119.5, 117.0, 116.7, 29.8; IR (neat) 3121, 2917, 2844, 1687, 1678, 1673, 1666, 1605, 1519, 1514, 1503, 1494, 1468, 1462, 1450, 1432; HRMS (ESI) calcd for $C_{14}H_9FN_2O$: 240.0699, found 241.0767 (M+H). The structure of compound **9** was confirmed by X-ray crystallography; see section **5**: Crystallographic data for compound **9**.

1-(3-Methylphenyl)- *N-tert*-butoxycarbonyl-L-tryptophan methyl ester (10a)

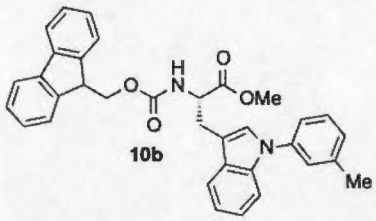


10a

Method C was followed on a 0.16 mmol scale starting from *N-tert*-butoxycarbonyl-L-tryptophan methyl ester and **3c**. The crude product was purified on silica gel (20% EtOAc/hexanes) to afford **10a** as a yellow oil (57 mg, 87%): R_f 0.33 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.51 (d, J = 7.0 Hz, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.32-7.27 (m, 1H), 7.19-7.16 (m, 2H), 7.13-7.05 (m, 4H), 5.05 (d, J = 8.3 Hz, 1H), 4.62-4.60 (m, 1H), 3.62 (s, 3H), 3.32-3.18 (m, 2H), 2.35 (s, 3H), 1.35 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.8, 155.3, 139.7, 139.5, 136.1, 129.4, 129.1, 127.2, 126.6, 124.9, 122.6, 121.3, 120.2, 119.1, 111.2, 110.7, 79.9, 54.1, 52.4, 28.4, 27.9, 21.5; IR (neat) 3433, 3377, 3050, 2976, 2928, 1743, 1709, 1606, 1590, 1494, 1493, 1459, 1365, 1159; HRMS (ESI) calcd for $C_{24}H_{28}N_2O_4$: 408.2049, found 353.1502 (M-C$(CH_3)_3$), 431.1941 (M+Na).

P. Petiot, J. Dansereau and A. Gagnon

1-(3-Methylphenyl)-Fmoc-D-tryptophan-methyl ester (10b)

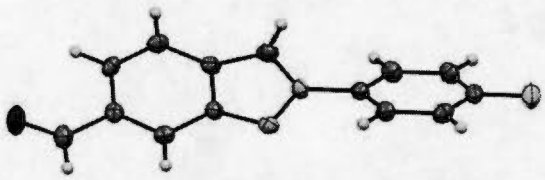


Method C was followed on a 0.11 mmol scale starting from *N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-tryptophan methyl ester and **3c**. The crude product was purified on silica gel (20% EtOAc/hexanes) to afford **10b** as a yellow oil (47 mg, 80%): R_f 0.29 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J = 7.4 Hz, 2H), 7.76-7.66 (m, 5H), 7.55-7.48 (m, 3H), 7.41-7.36 (m, 4H), 7.34-7.26 (m, 3H), 5.56 (d, J = 8.3 Hz, 1H), 4.96-4.90 (m, 1H), 4.58-4.49 (m, 2H), 4.36-4.33 (m, 1H), 3.86 (s, 3H), 3.51 (d, J = 5.4 Hz, 2H), 2.56 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.4, 155.8, 143.9, 143.8, 141.3, 139.7, 139.5, 136.1, 129.5, 127.7, 127.3, 127.1, 126.7, 125.2, 125.0, 122.7, 121.4, 120.3, 120.0, 119.0, 110.8, 67.1, 54.6, 52.5, 47.2, 28.0, 21.5; IR (neat) 3418, 3356, 3049, 2950, 1717, 1606, 1589, 1494, 1459, 1207.

5. Crystallographic data for compound 8b

CCDC-986210 (for **8b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystal Structure Report for compound 8b



A light orange needle-like specimen of $C_{14}H_9FN_2O$, approximate dimensions 0.047 mm x 0.058 mm x 0.268 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 5856 frames were collected. The total exposure time was 16.27 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 15339 reflections to a maximum θ angle of 68.37° (0.83 Å resolution), of which 1971 were independent (average redundancy 7.782, completeness = 99.8%, R_{int} = 5.15%) and 1661 (84.27%) were greater than $2\sigma(F^2)$. The final cell constants of a = 3.76530(10) Å, b = 17.7911(4) Å, c = 16.0214(3) Å, β = 92.874(2)°, volume = 1071.90(4) Å^3, are based upon the refinement of the XYZ-centroids of 9053 reflections above 20 σ(I) with 7.430° < 2θ < 136.7°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.930. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.7940 and 0.9590.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P $2_1/c$, with Z = 4 for the formula unit $C_{14}H_9FN_2O$. The final anisotropic full-matrix least-squares refinement on F^2 with 164 variables converged at R_1 = 5.83%, for the observed data and wR_2 = 16.57% for all data. The goodness-of-fit was 1.193. The largest peak in the final difference electron density synthesis was 0.358 e$^-$/Å^3 and the largest hole was -0.276 e$^-$/Å^3 with an RMS deviation of 0.074 e$^-$/Å^3. On the basis of the final model, the calculated density was 1.489 g/cm^3 and F(000) 496 e$^-$.

Table 1. Sample and crystal data for Pauline1b.

CCDC deposition number	986210	
Chemical formula	$C_{14}H_9FN_2O$	
Formula weight	240.23	
Temperature	150(2) K	
Wavelength	1.54178 Å	
Crystal size	0.047 x 0.058 x 0.268 mm	
Crystal habit	light orange needle	
Crystal system	monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 3.76530(10) Å	α = 90°
	b = 17.7911(4) Å	β = 92.874(2)°

	c = 16.0214(3) Å	γ = 90°
Volume	1071.90(4) Å^3	
Z	4	
Density (calculated)	1.489 g/cm^3	
Absorption coefficient	0.900 mm^{-1}	
F(000)	496	

Table 2. Data collection and structure refinement for Pauline1b.

Theta range for data collection	3.71 to 68.37°	
Index ranges	-4<=h<=4, -21<=k<=21, -19<=l<=19	
Reflections collected	15339	
Independent reflections	1971 [R(int) = 0.0515]	
Coverage of independent reflections	99.8%	
Absorption correction	multi-scan	
Max. and min. transmission	0.9590 and 0.7940	
Structure solution technique	direct methods	
Structure solution program	SHELXS-97 (Sheldrick, 2008)	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2013 (Sheldrick, 2013)	
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	1971 / 0 / 164	
Goodness-of-fit on F^2	1.193	
Final R indices	1661 data; I>2σ(I)	$R_1 = 0.0583$, $wR_2 = 0.1595$
	all data	$R_1 = 0.0682$, $wR_2 = 0.1657$
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0789P)^2+0.9563P]$ where $P=(F_o^2+2F_c^2)/3$	
Extinction coefficient	0.0028(8)	
Largest diff. peak and hole	0.358 and -0.276 eÅ^{-3}	
R.M.S. deviation from mean	0.074 eÅ^{-3}	

Atomic coordinates, bond lengths, bond angles, torsion angles, anisotropic atomic displacement parameters are provided in the attached CIF file, which can also be retrieved from the Cambridge Crystallographic Data Centre using deposition number 986210 at the following URL: http://www.ccdc.cam.ac.uk/Community/Requestastructure/Pages/Requestastructure.aspx

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Datablock: I

No errors found in this datablock

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               alpha=90          beta=92.874(2)    gamma=90
Temperature: 150 K
                      Calculated                    Reported
Volume                1071.91(4)                    1071.90(4)
Space group           P 21/c                        P 21/c
Hall group            -P 2ybc                       -P 2ybc
Moiety formula        C14 H9 F N2 O                 C14 H9 F N2 O
Sum formula           C14 H9 F N2 O                 C14 H9 F N2 O
Mr                    240.23                        240.23
Dx,g cm-3             1.489                         1.489
Z                     4                             4
Mu (mm-1)             0.900                         0.900
F000                  496.0                         496.0
F000'                 497.66
h,k,lmax              4,21,19                       4,21,19
Nref                  1975                          1971
Tmin,Tmax             0.939,0.959
Tmin'                 0.786
Correction method= Not given
Data completeness= 0.998          Theta(max)= 68.371
R(reflections)= 0.0583( 1661)         wR2(reflections)= 0.1657( 1971)
S = 1.193               Npar= 164
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Alert level G

PUBL017_ALERT_1_G The _publ_section_references section is missing or empty.

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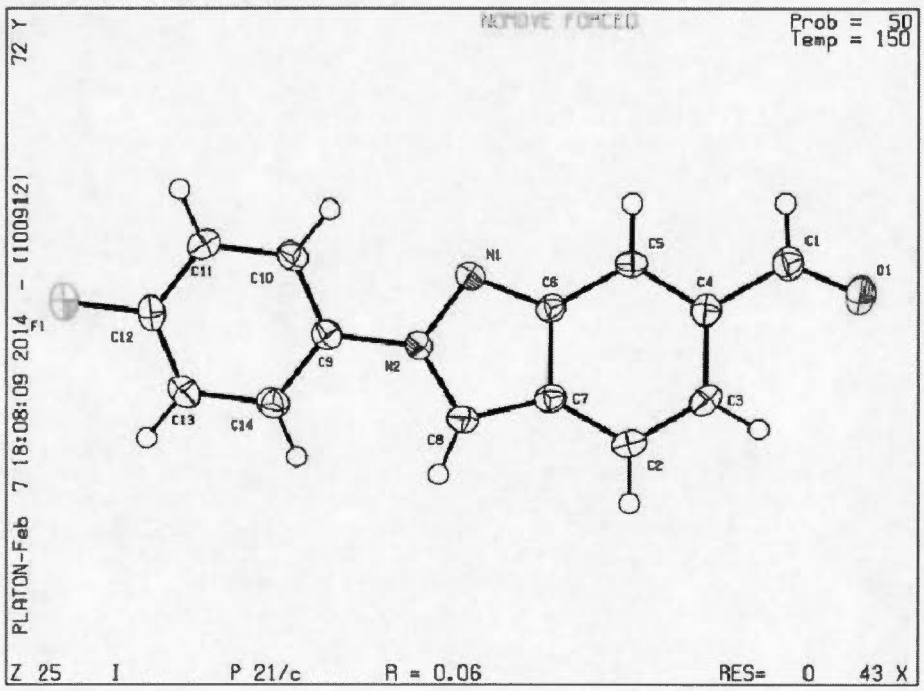

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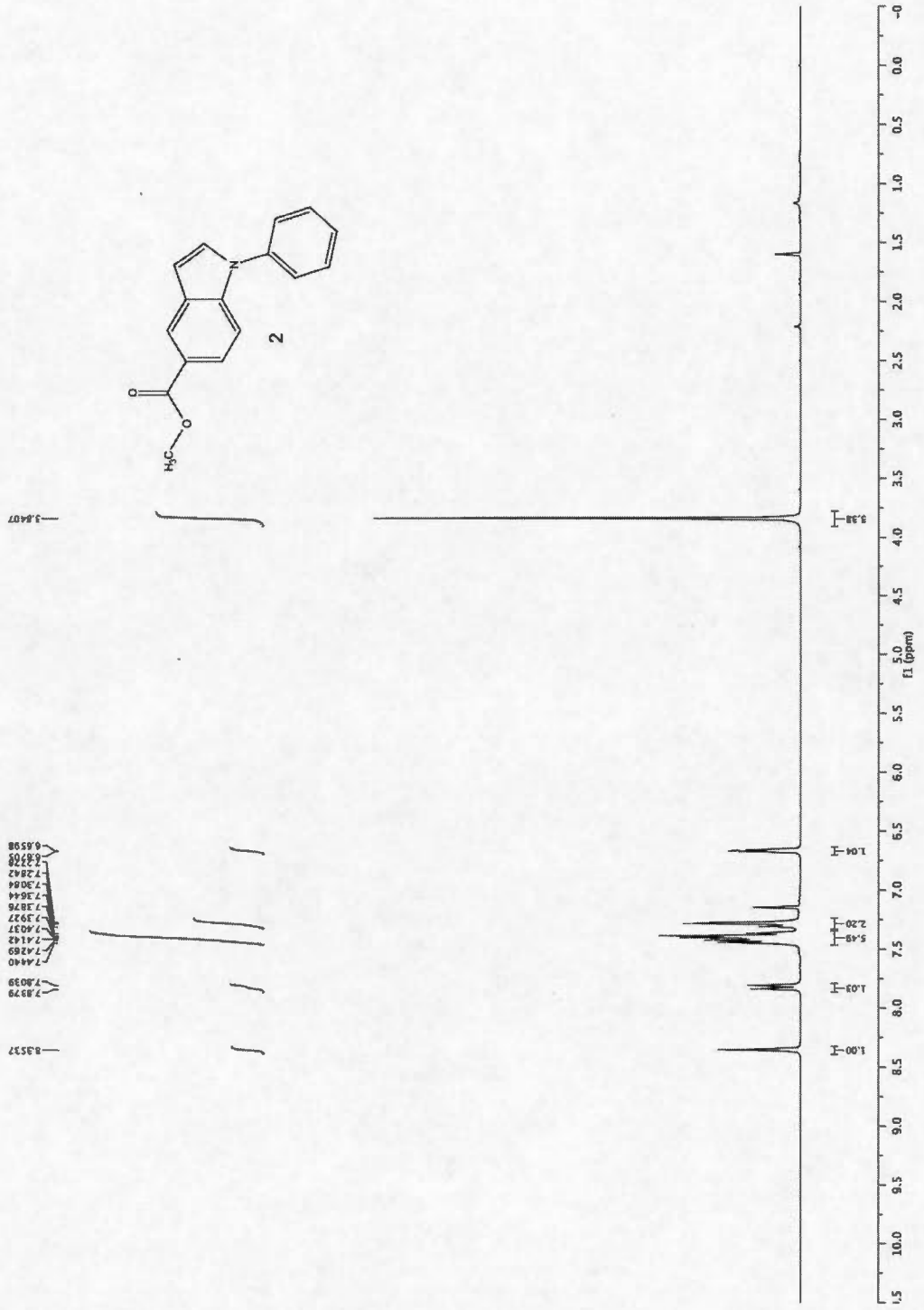
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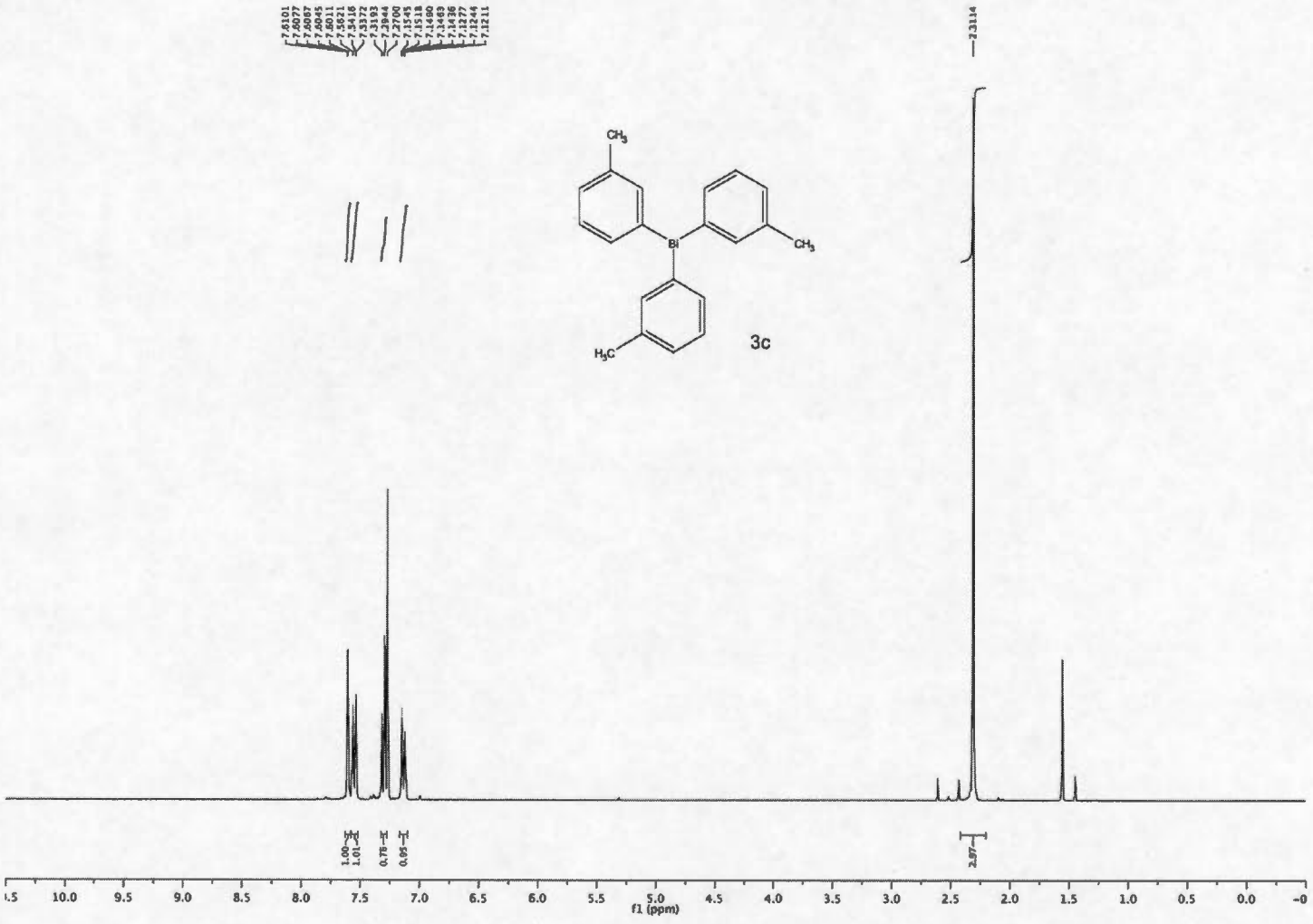
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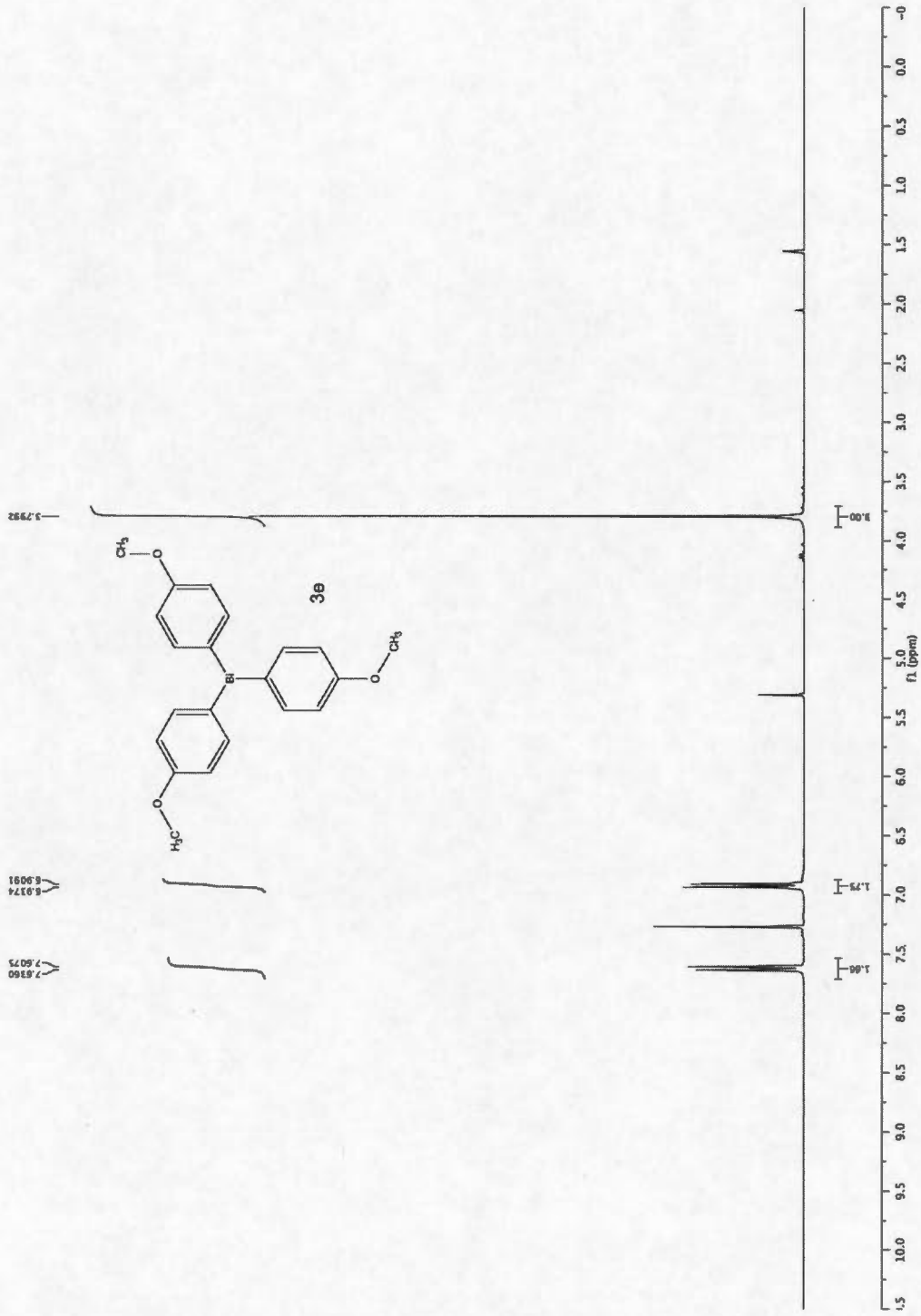
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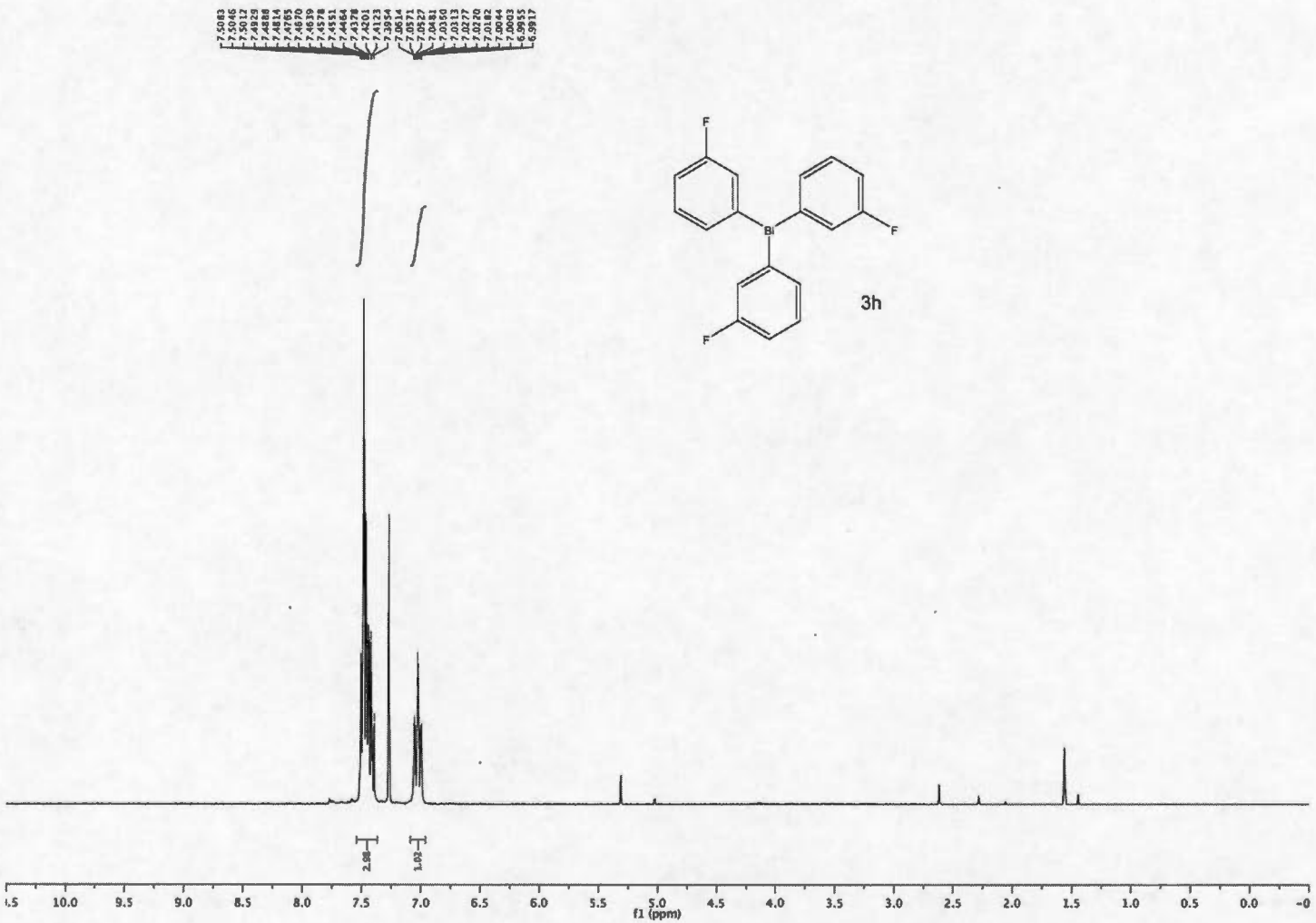
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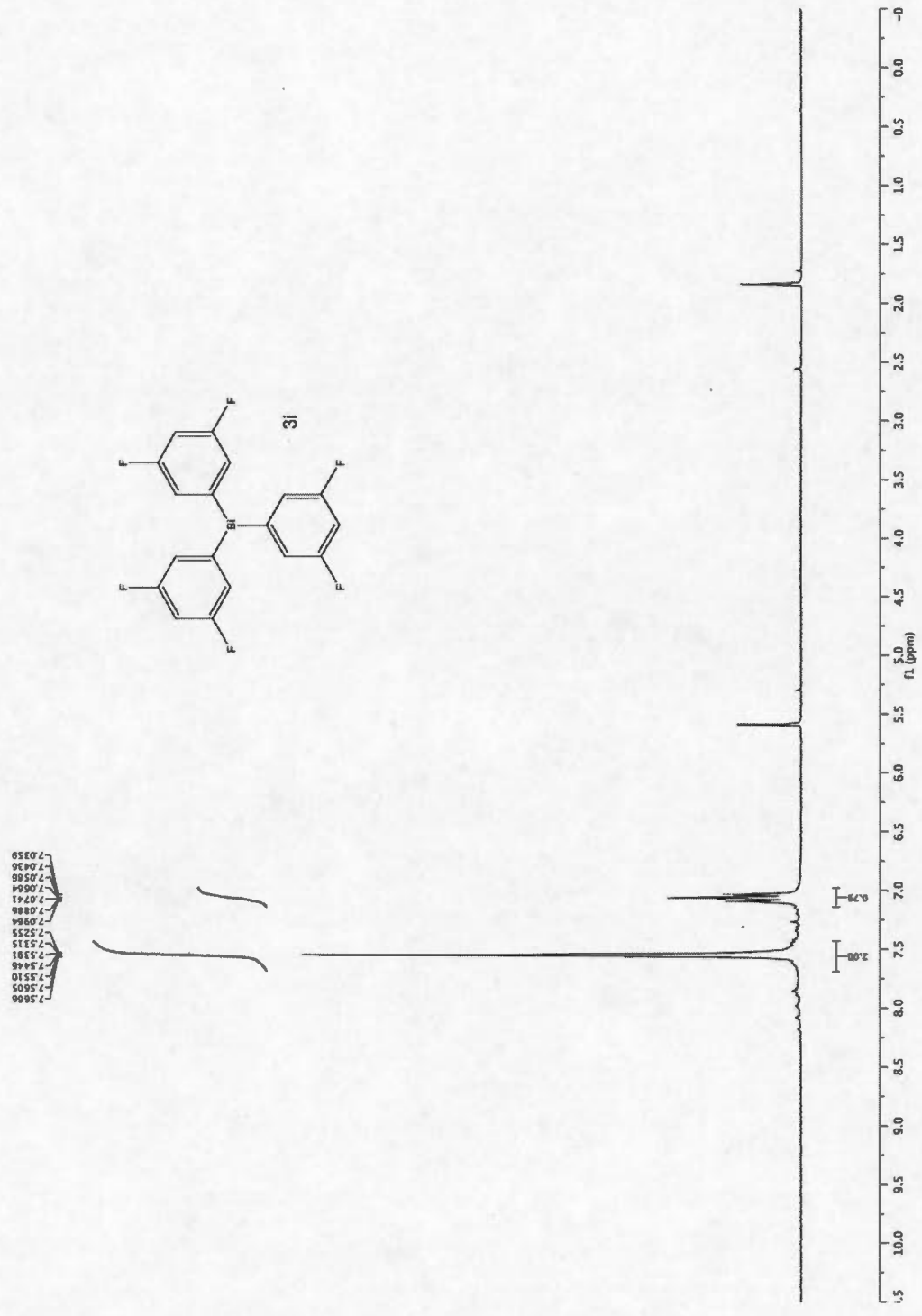
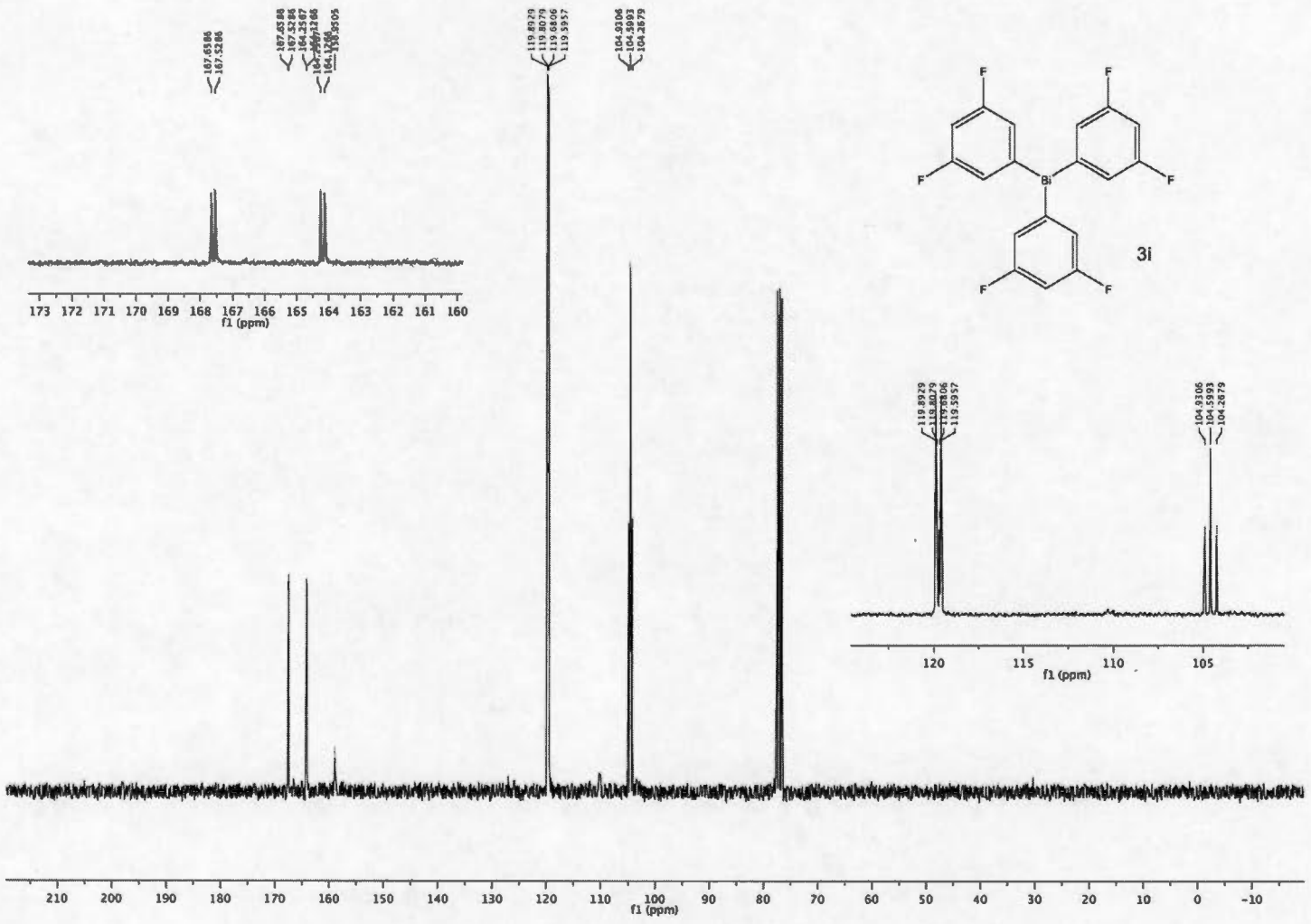
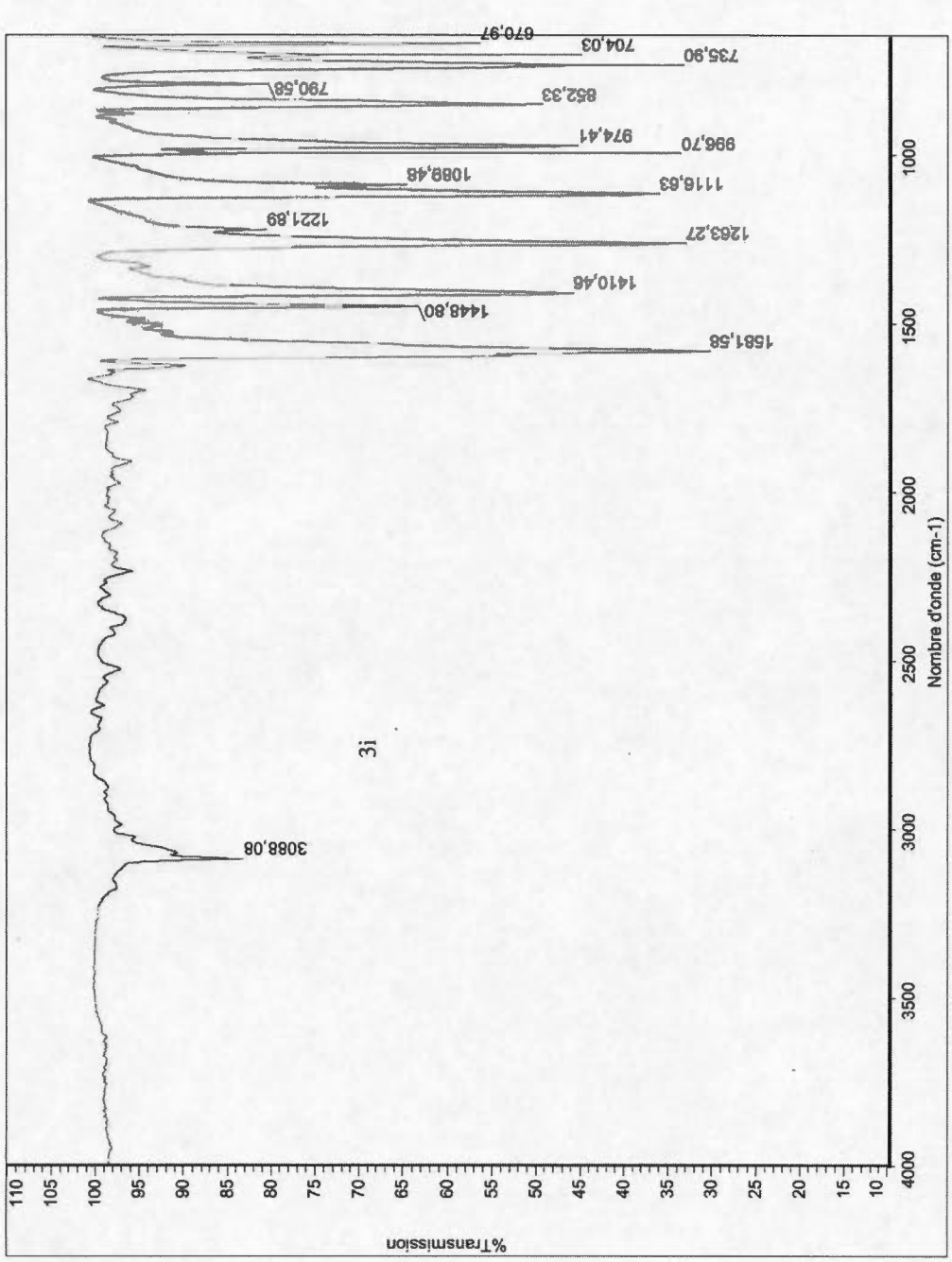
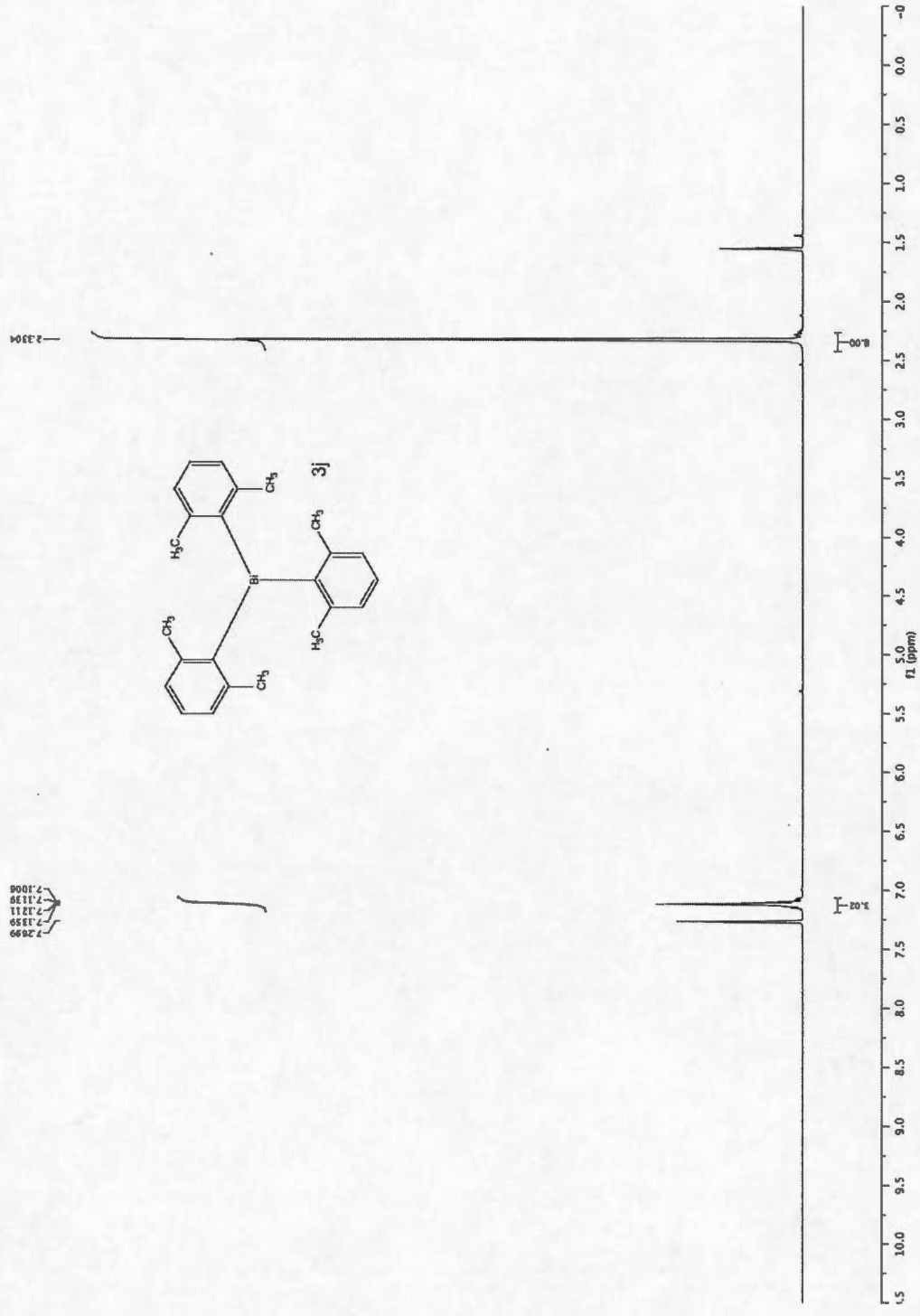
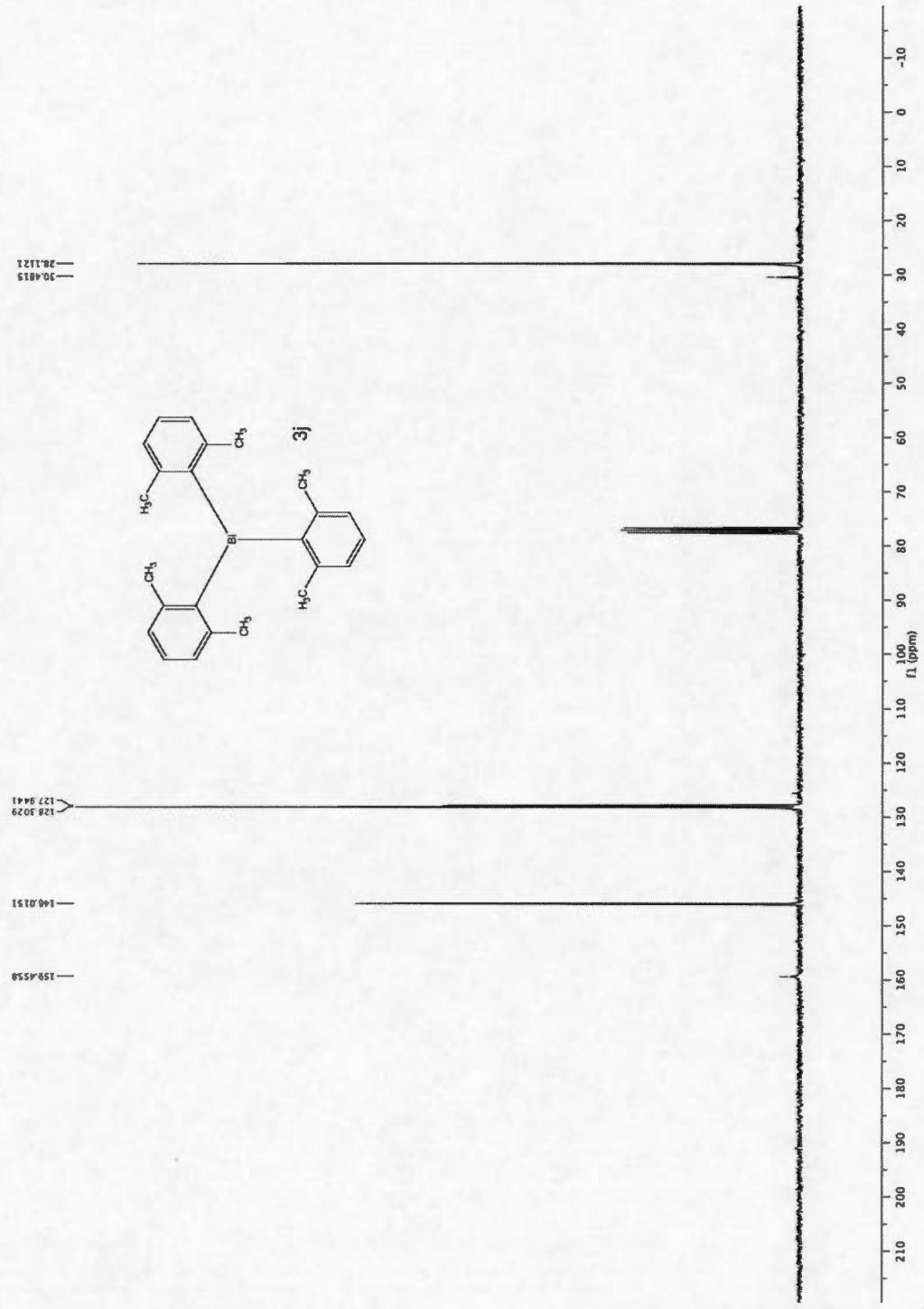
7.0350
7.0313
7.0277
7.0220
7.0182
7.0044
7.0003
6.9955
6.9917
F
Bi
F
F
3h
2.98
1.03
f1 (ppm)

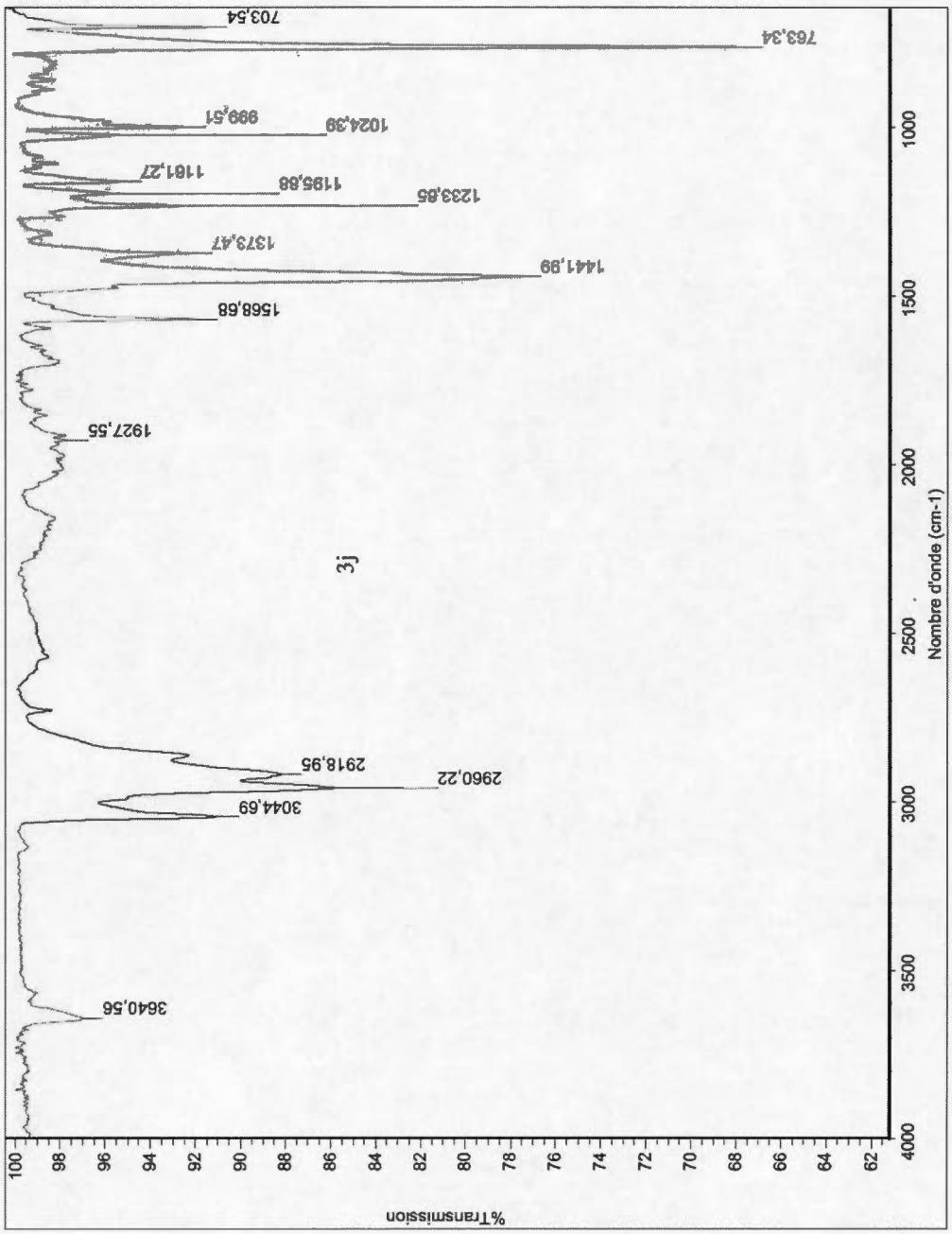

3i
F
F
F
F
F
F
Bi
7.5666
7.5605
7.3510
7.3446
7.3381
7.3315
7.3255
7.0984
7.0886
7.0741
7.0654
7.0588
7.0436
7.0359
6.79
3.00
f1 (ppm)

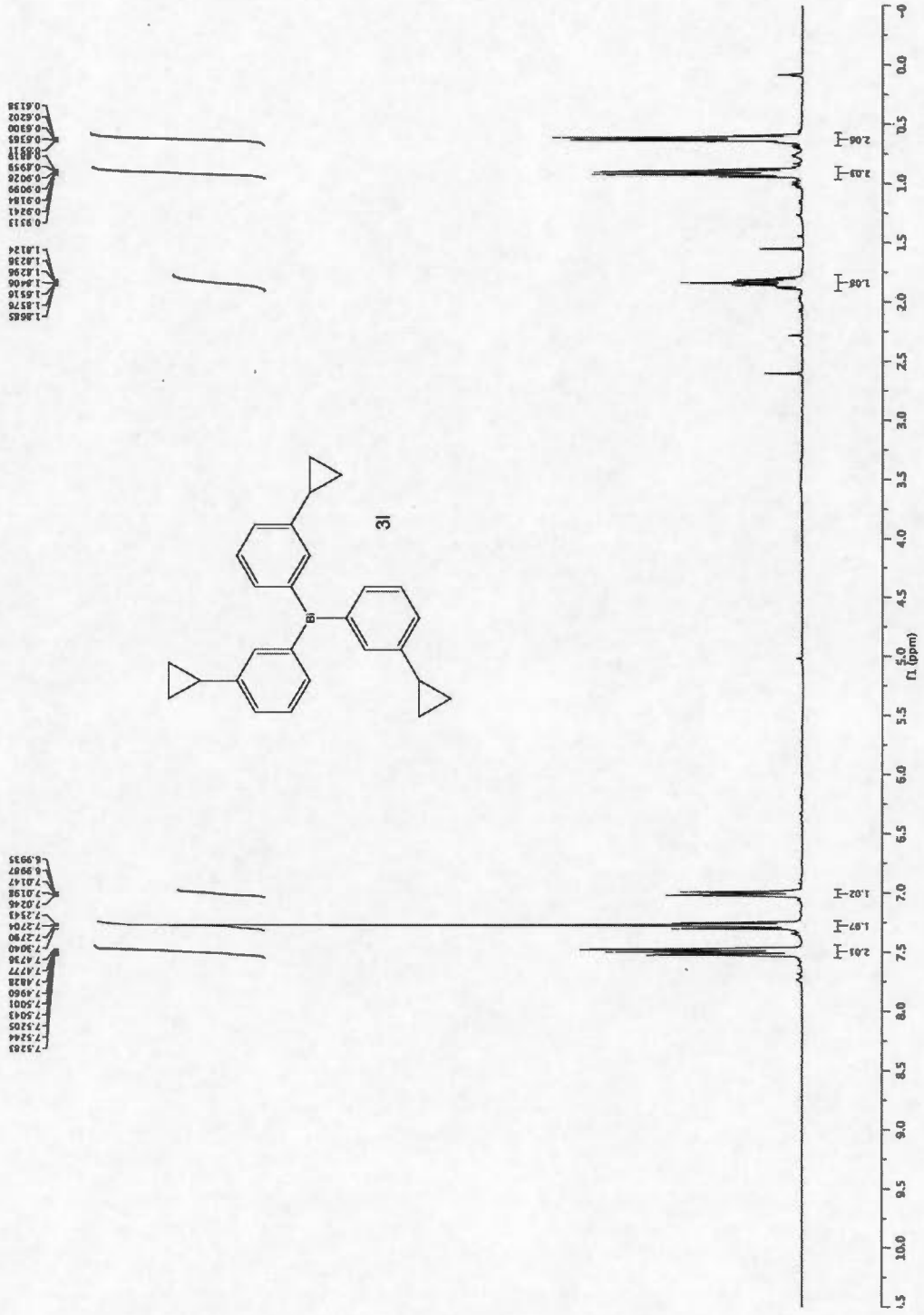

167.6586
167.5286
164.2567
164.1286
119.8929
119.8079
119.6406
119.5957
104.9306
104.5993
104.2679
3i
F
Bi
173 172 171 170 169 168 167 166 165 164 163 162 161 160
f1 (ppm)
120 115 110 105
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

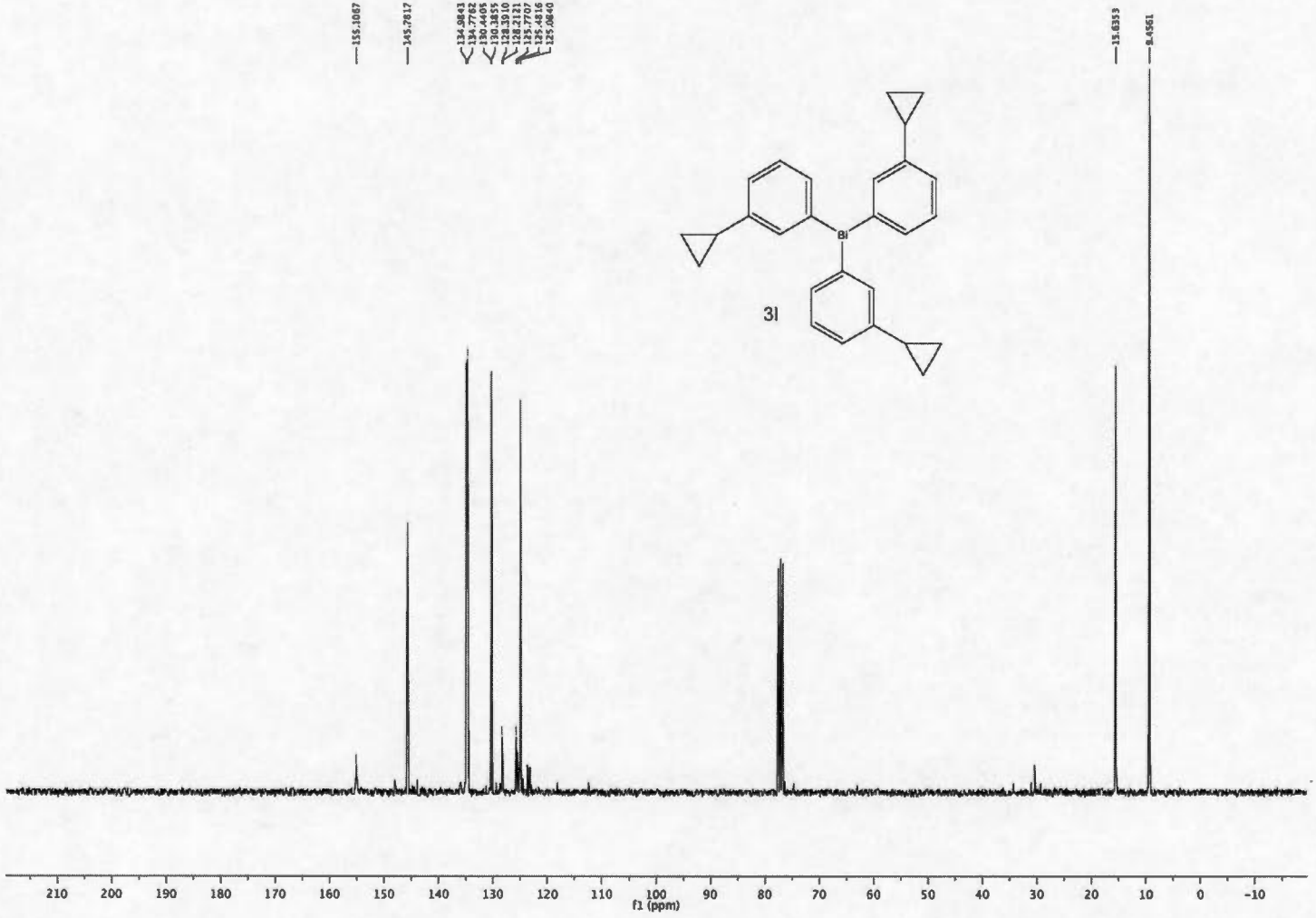

%Transmission
Nombre d'onde (cm-1)
3i
3088,08
1581,58
1448,80
1410,46
1263,27
1221,89
1116,63
1088,48
996,70
974,41
852,33
790,58
735,90
704,03
670,97

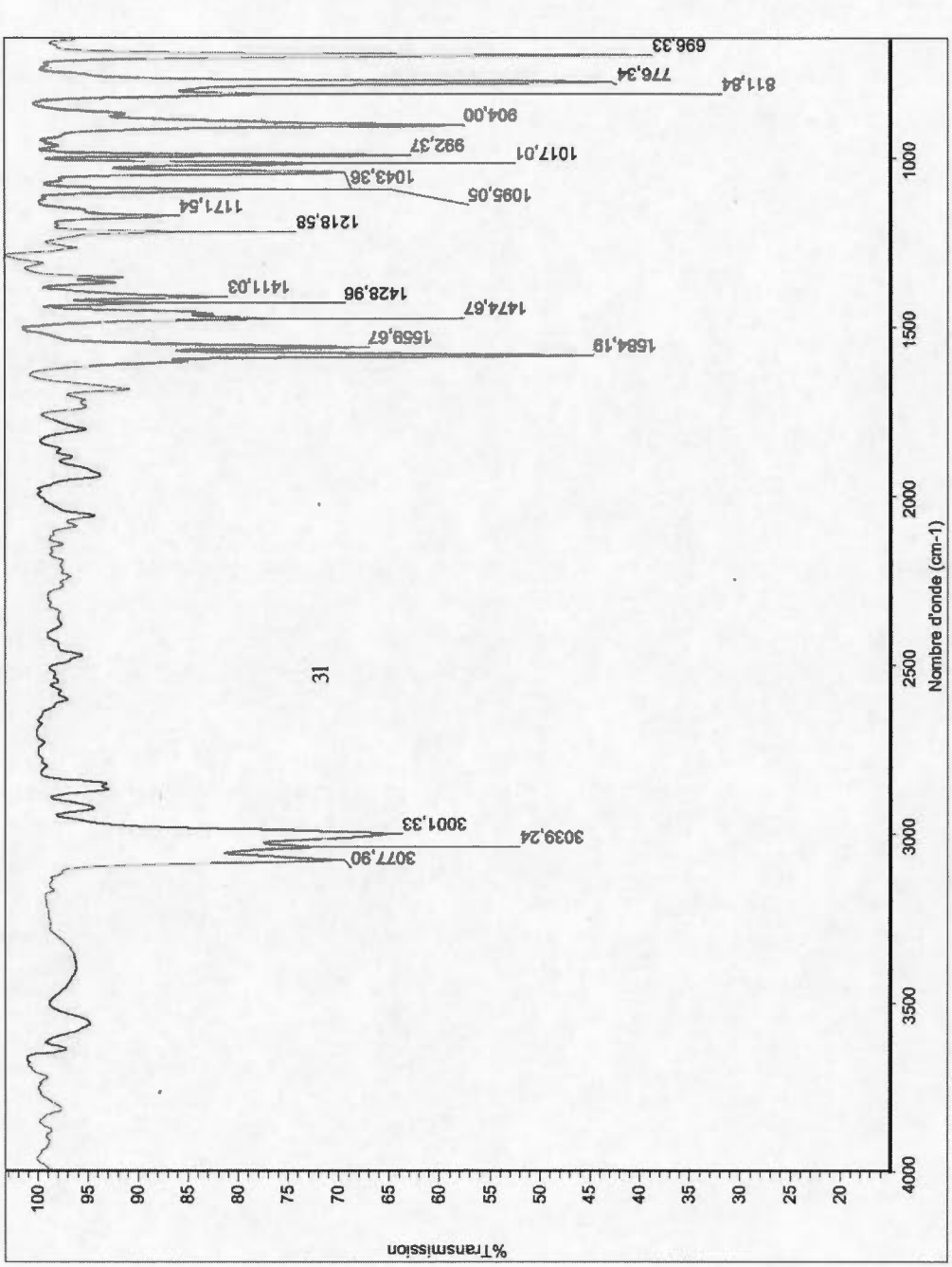

2.3304
7.2899
7.2359
7.2211
7.1139
7.1006
8.00
3.02
f1 (ppm)
3j
Bi
CH3
H3C

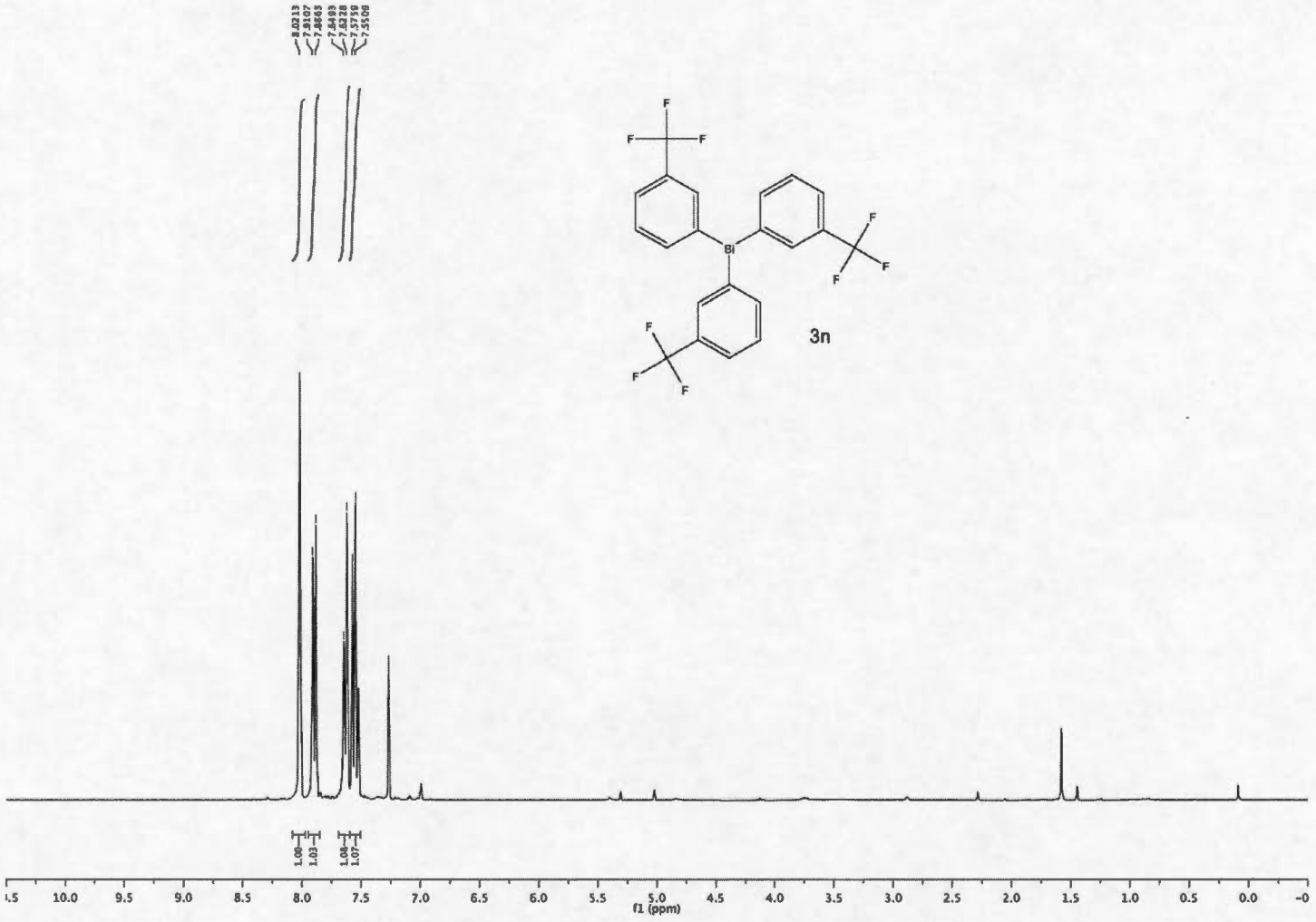

3j
Bi
CH3
H3C
28.1121
30.4815
128.3029
127.9441
146.0151
159.4558
f1 (ppm)

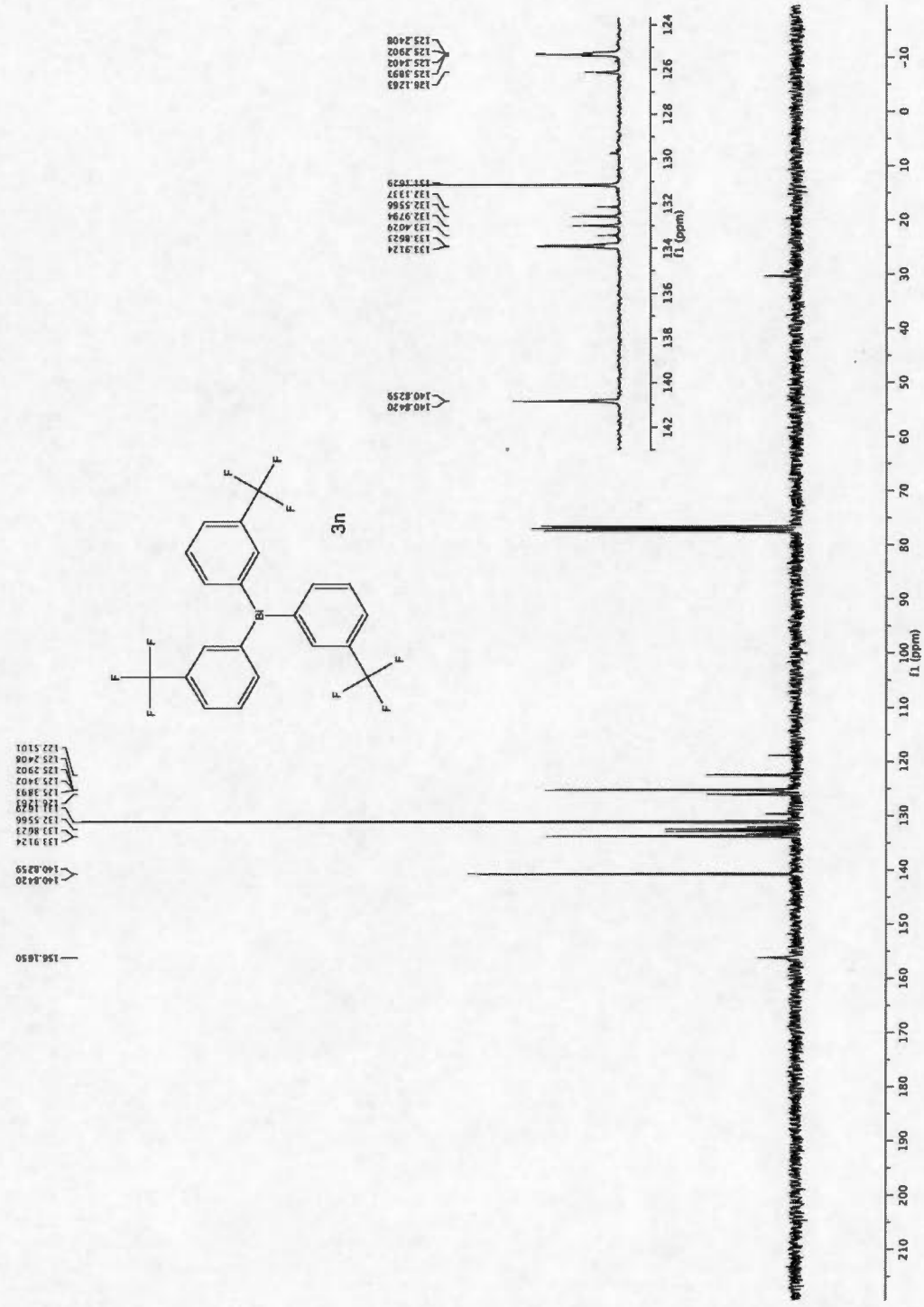

%Transmission
Nombre d'onde (cm-1)
3j
3640,56
3044,69
2960,22
2918,95
1927,55
1568,68
1441,89
1373,47
1233,85
1185,88
1181,27
1024,39
999,51
763,34
703,54

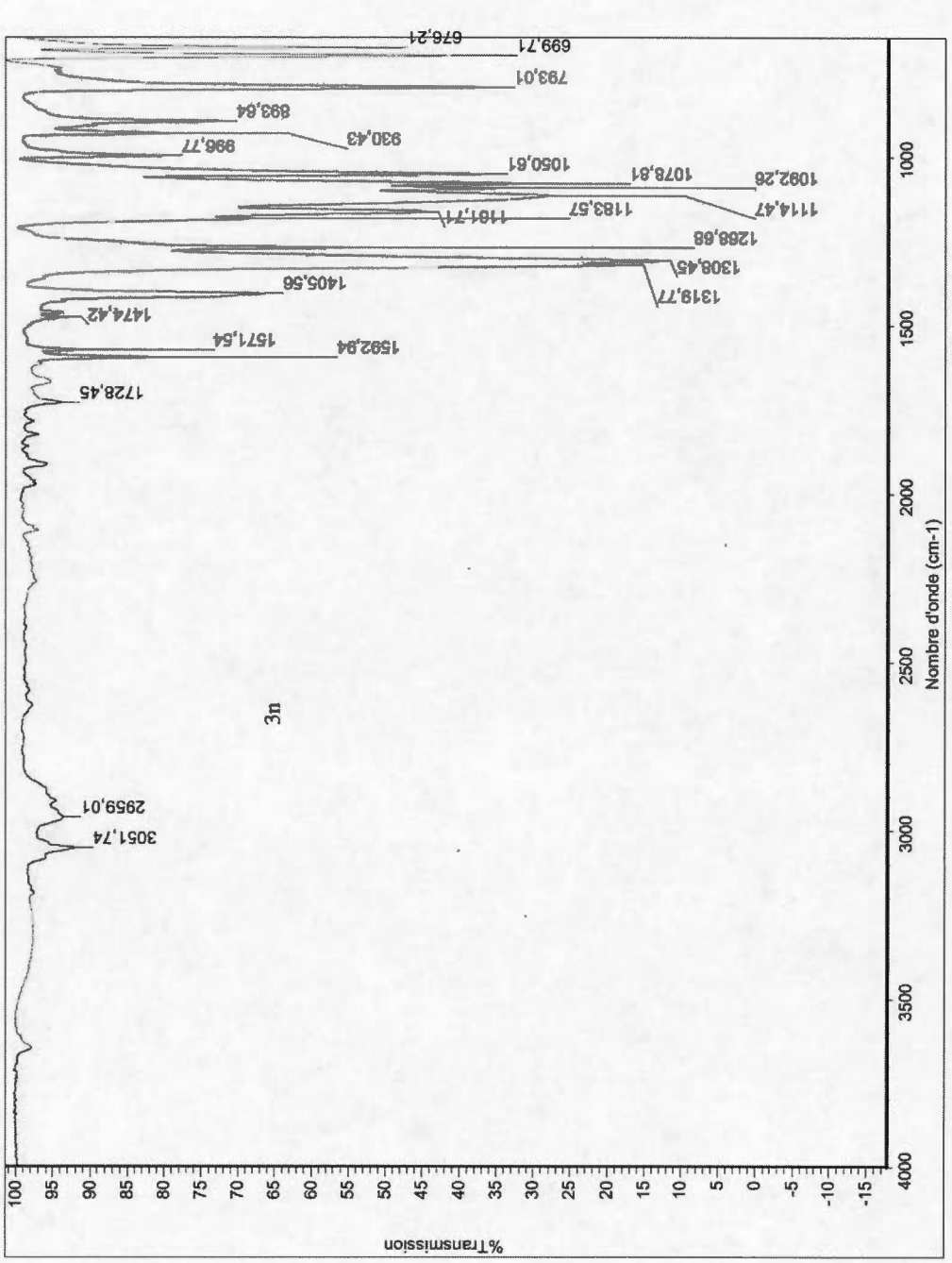

3l
Bi
f1 (ppm)

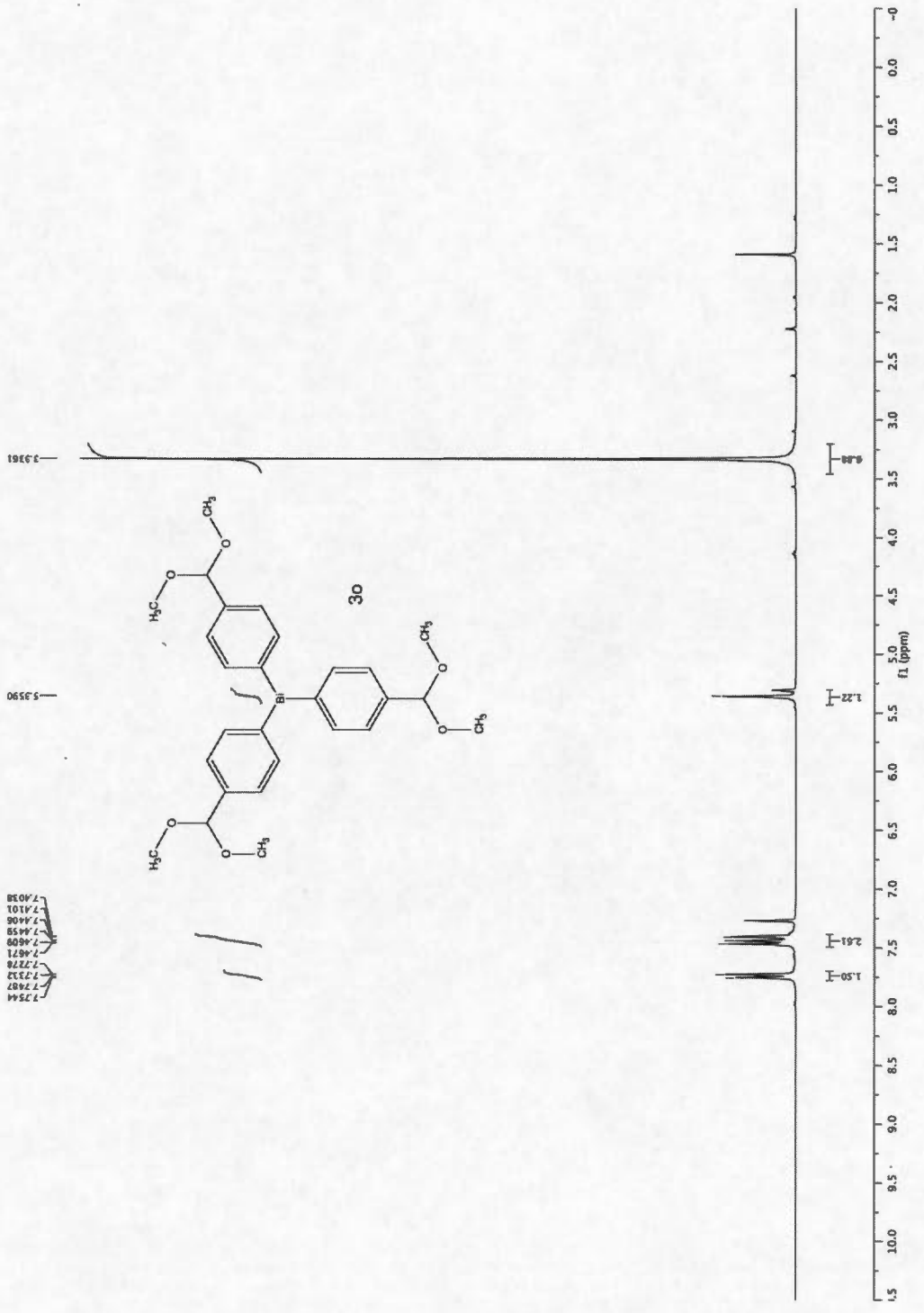

155.1067
145.7817
134.9843
134.7762
130.4405
130.1855
128.3910
128.2121
125.7707
125.4816
125.0840
15.6353
8.4561
Bi
3l
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

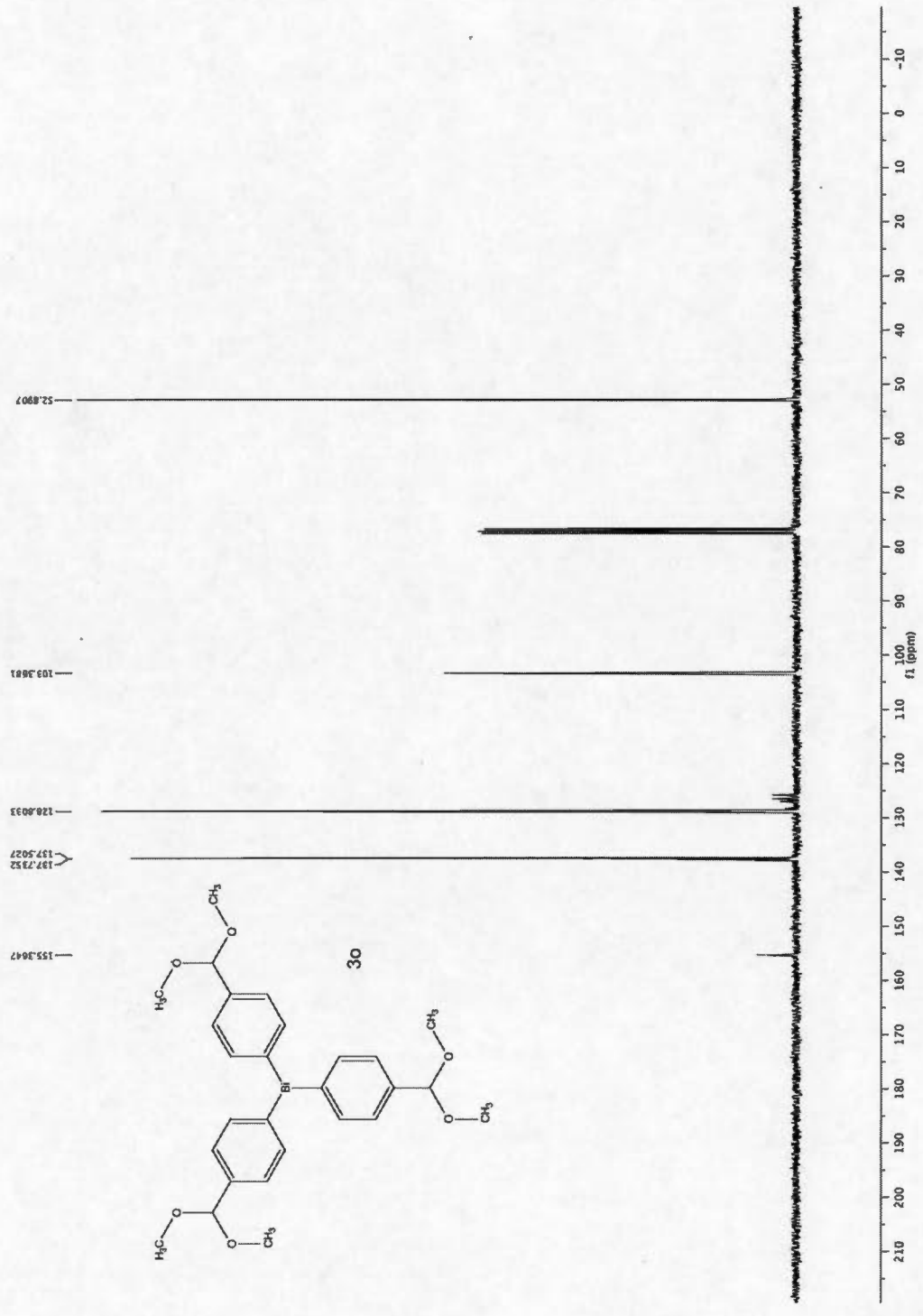

%Transmission
Nombre d'onde (cm-1)
4000
3500
3000
2500
2000
1500
1000
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
3077,90
3039,24
3001,33
1584,19
1559,67
1474,67
1428,96
1411,03
1218,58
1171,54
1095,05
1043,36
1017,01
992,37
904,00
811,84
776,34
696,33
31

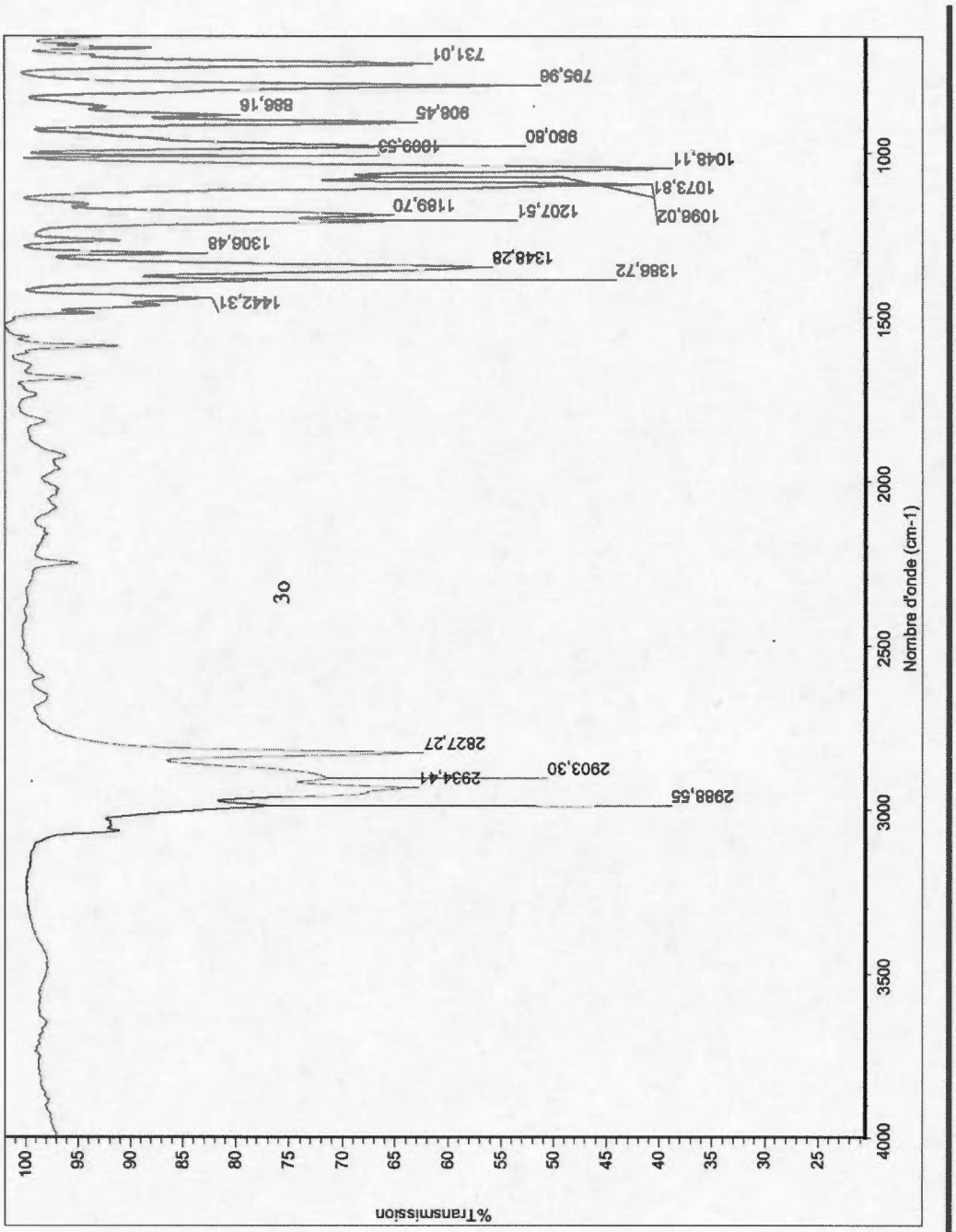

8.0213
7.9107
7.8665
7.5493
7.5328
7.5750
7.5508
F
F
F
Bi
F
F
F
F
F
3n
1.00
1.03
1.04
1.07
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

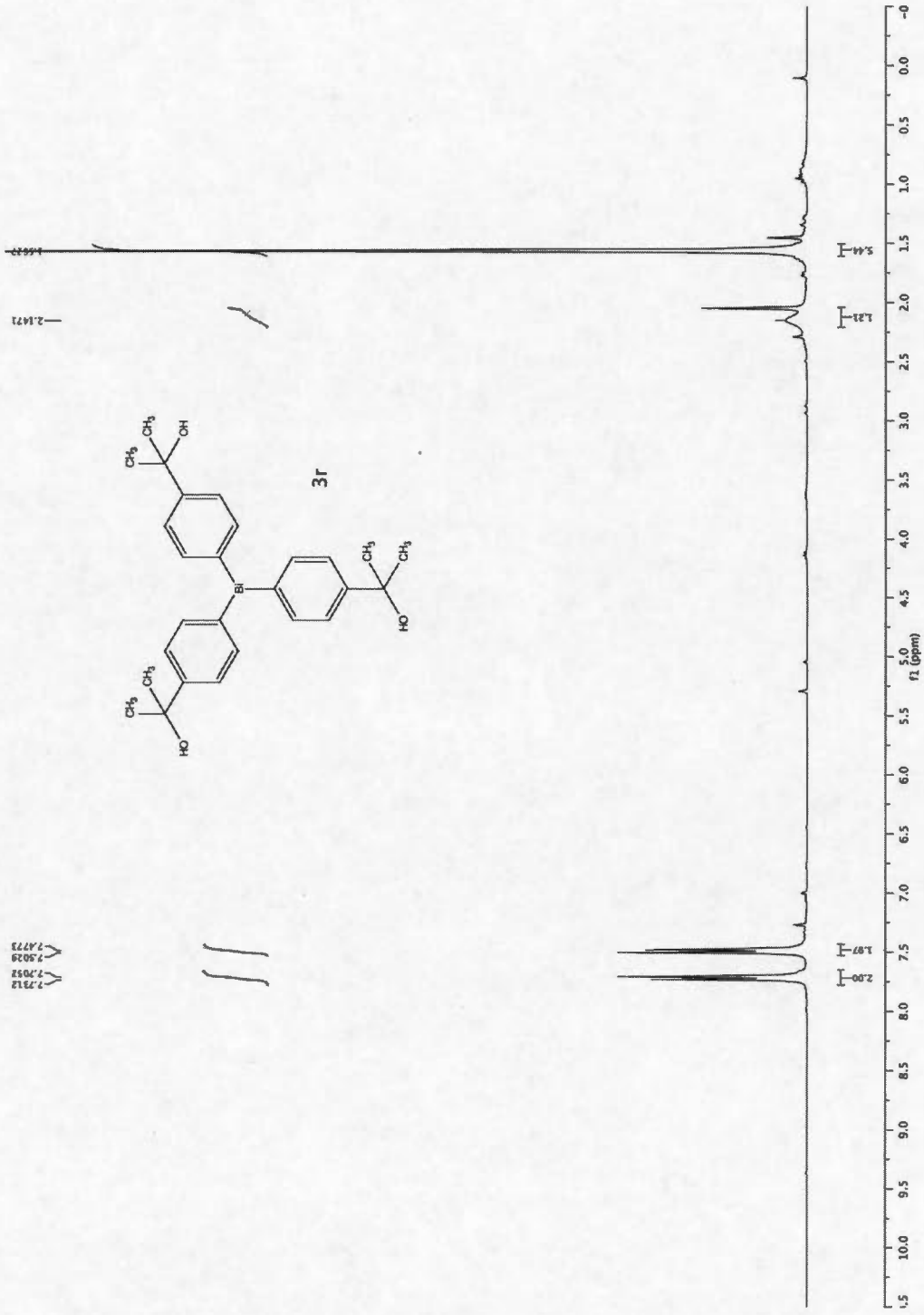

3n
Bi
F
156.1650
140.8420
140.8259
133.9124
133.8623
133.4029
132.9794
132.5566
132.1337
131.1029
126.1263
125.3893
125.3402
125.2902
125.2408
122.5101
f1 (ppm)

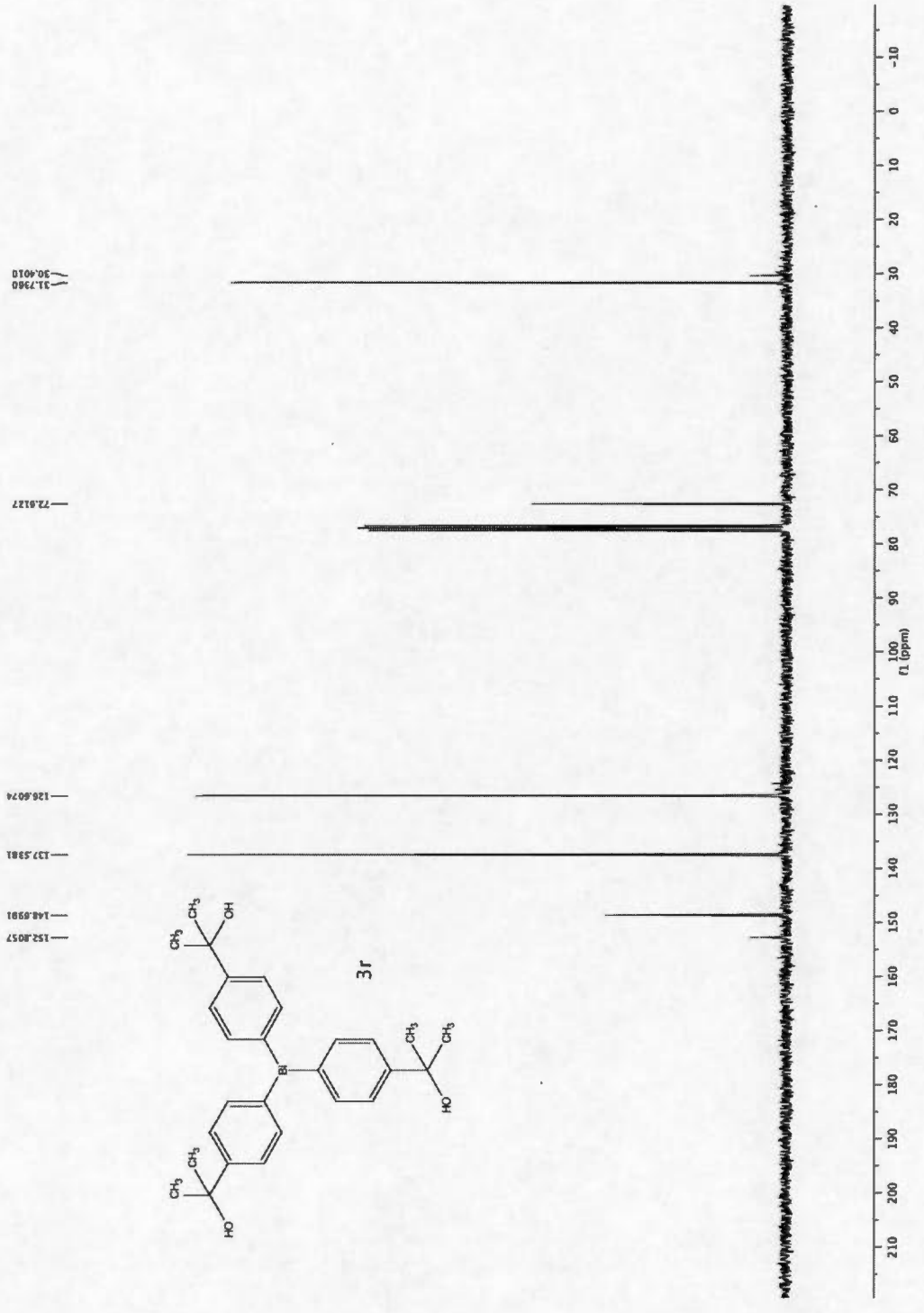

%Transmission
Nombre d'onde (cm-1)
3n
676,21
699,71
793,01
893,64
930,43
996,77
1050,61
1078,61
1092,26
1114,47
1181,71
1183,57
1268,68
1308,45
1319,77
1405,56
1474,42
1571,54
1592,94
1728,45
2959,01
3051,74

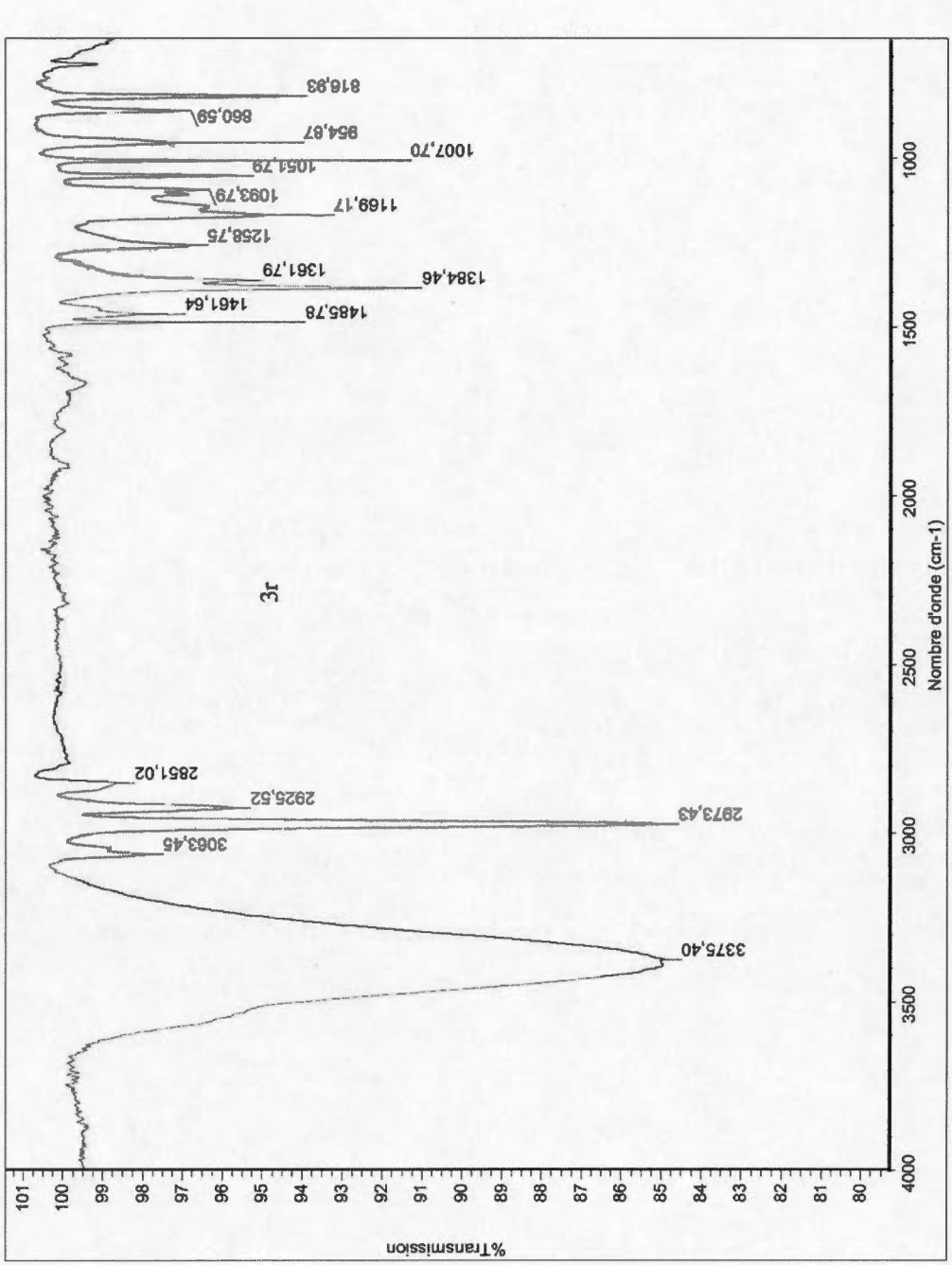

3.3361
5.3590
7.7544
7.7487
7.7332
7.7276
7.4671
7.4609
7.4459
7.4406
7.4101
7.4038
30
8.28
1.22
2.61
1.50
f1 (ppm)

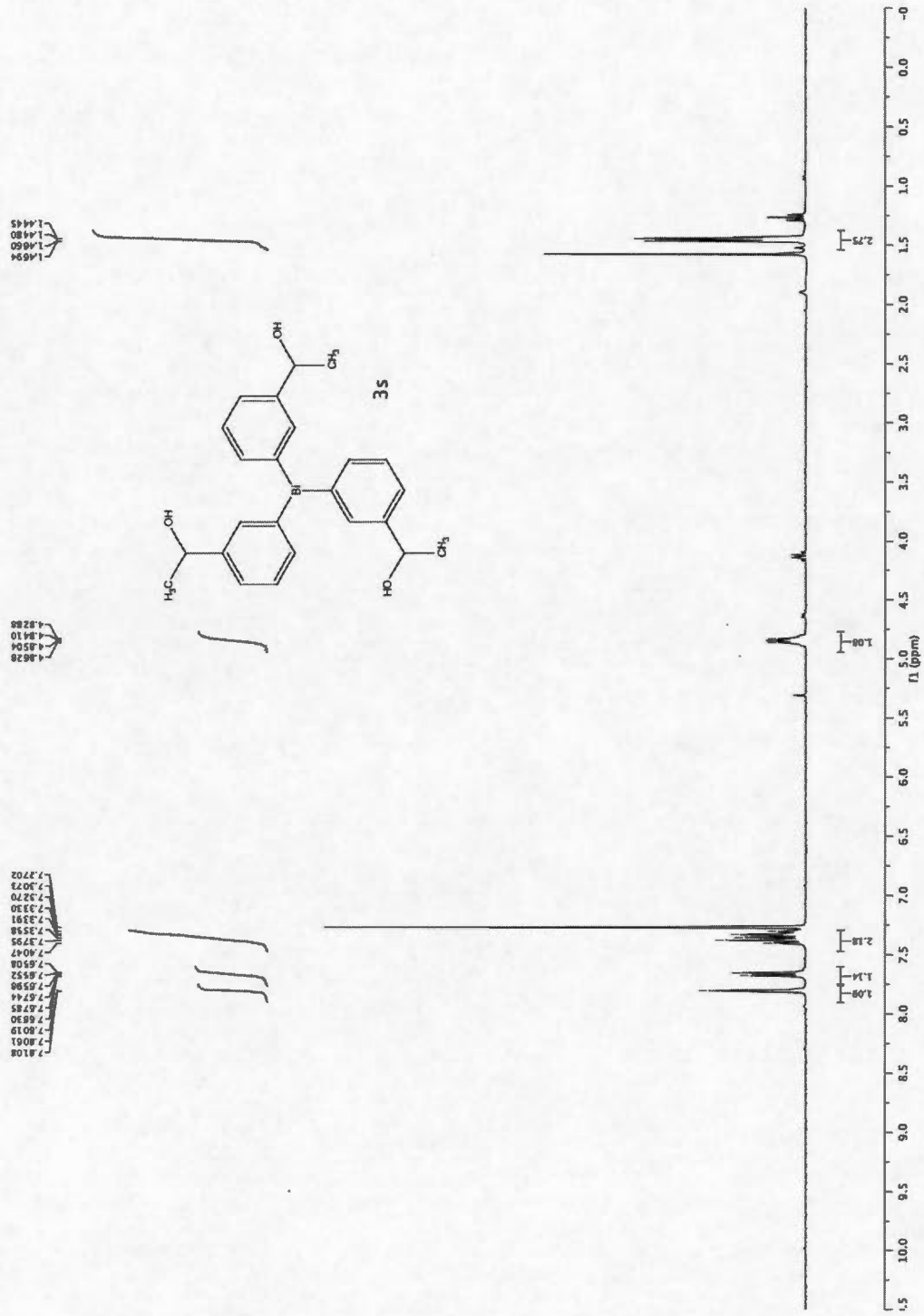

52.8907
103.3681
128.8033
137.7352
137.5027
155.3047
30
f1 (ppm)

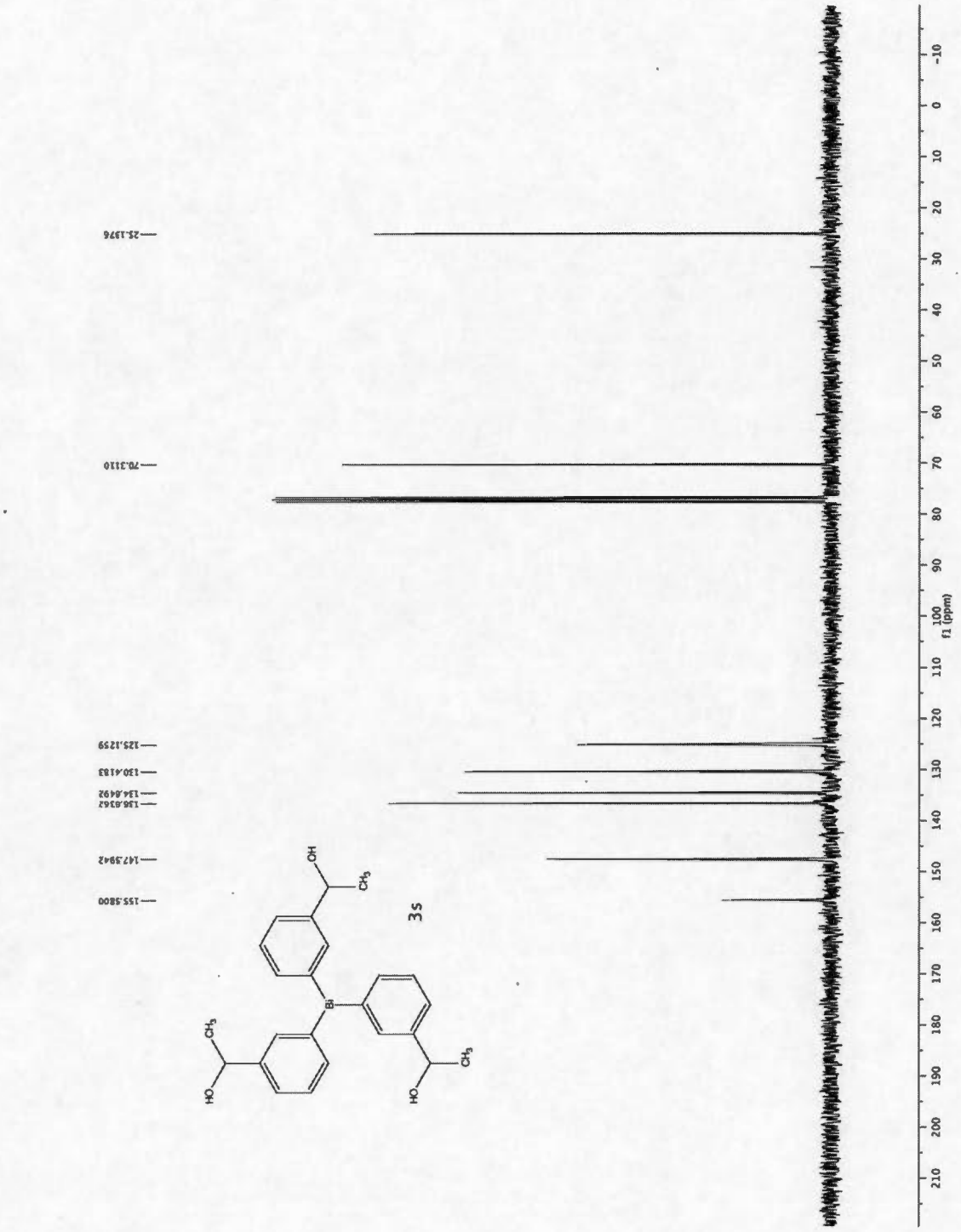

%Transmission
Nombre d'onde (cm-1)
3o
2988,55
2934,41
2903,30
2827,27
1442,31
1386,72
1348,28
1306,48
1207,51
1189,70
1098,02
1073,81
1048,11
1009,53
860,80
808,45
886,16
785,96
731,01

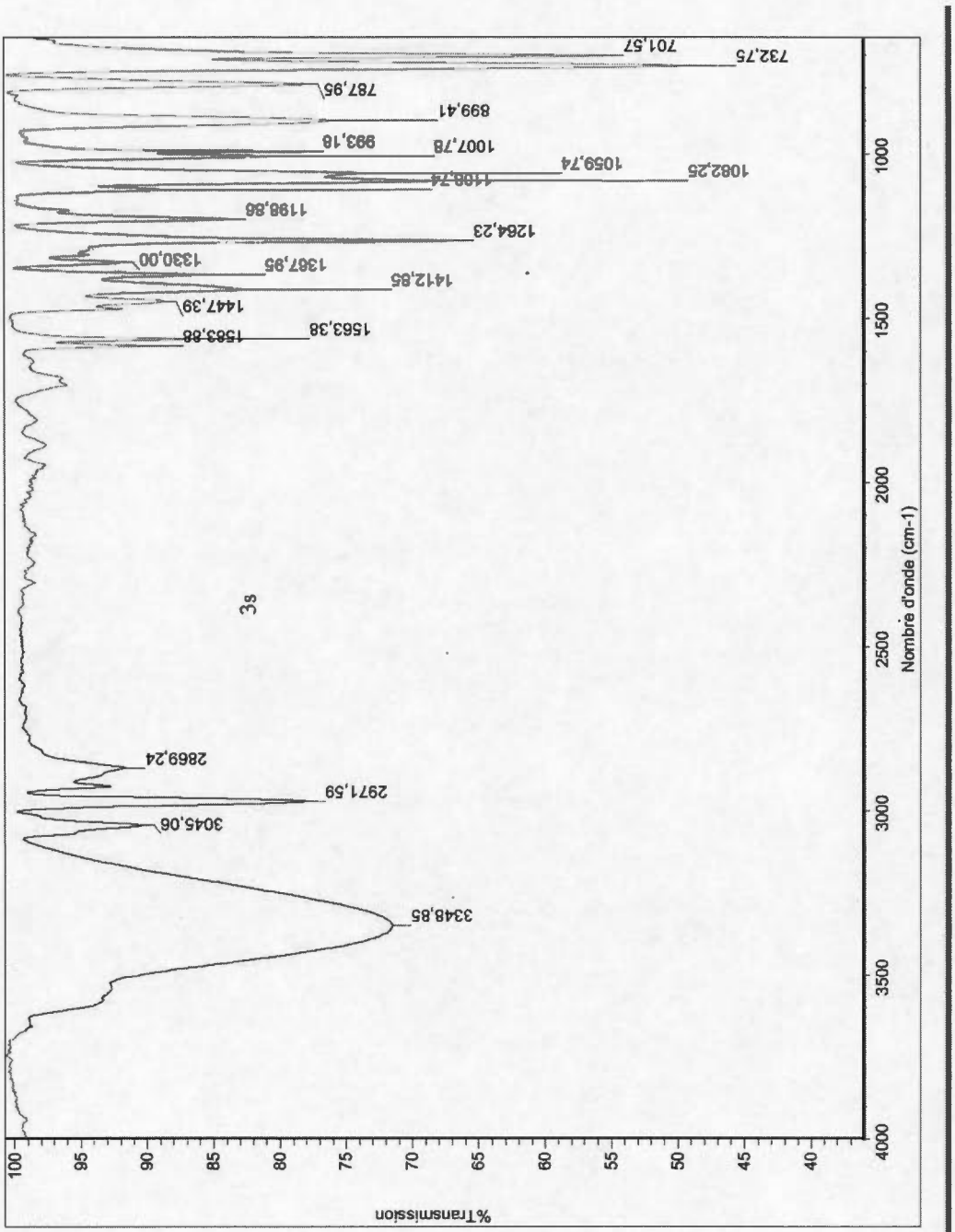

3r
f1 (ppm)


31.7960
30.4018
72.6127
126.6074
137.5381
148.6981
152.8057
3r
f1 (ppm)

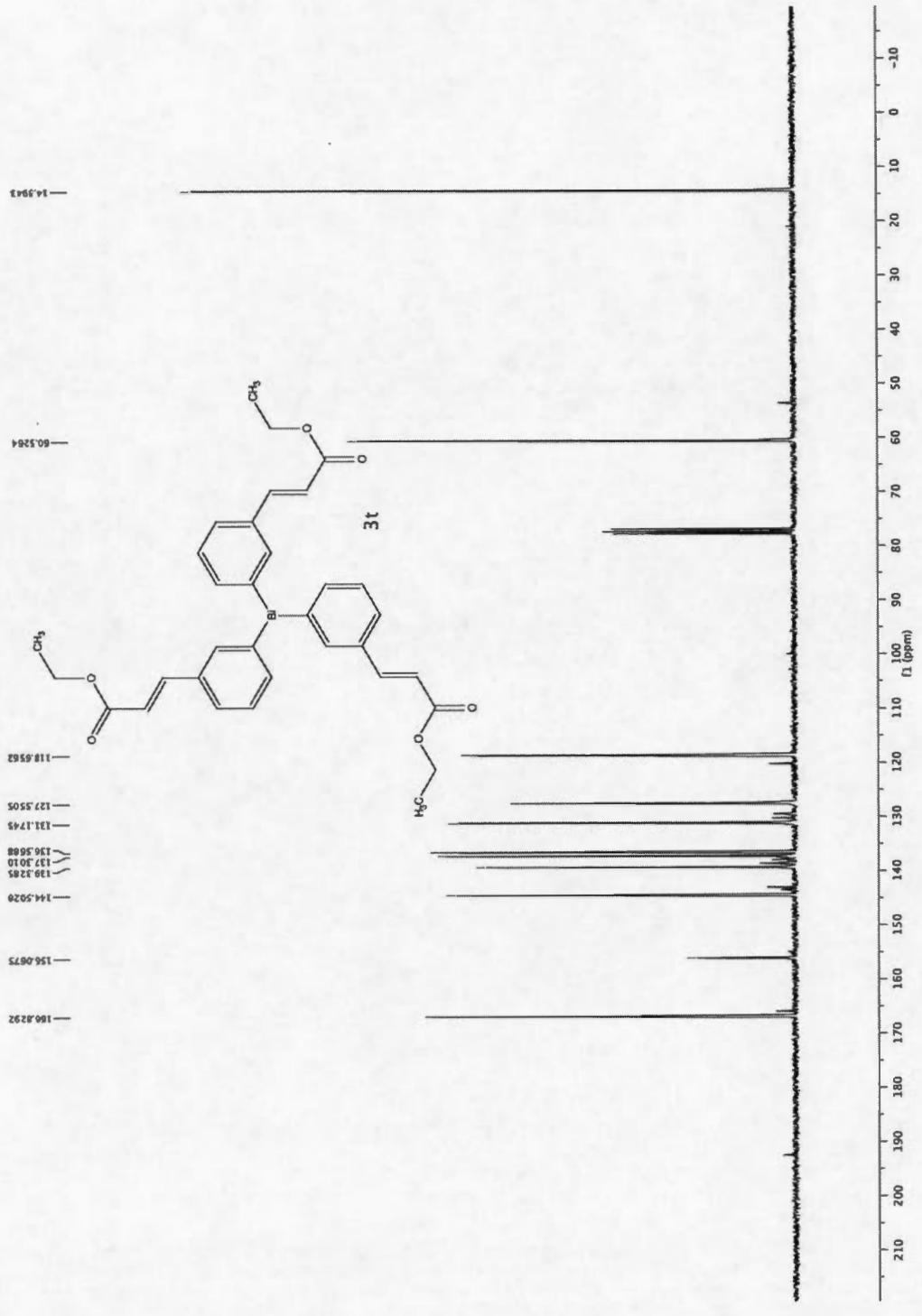

%Transmission
Nombre d'onde (cm-1)
3r
3375,40
3063,45
2973,43
2925,52
2851,02
1485,78
1461,64
1384,46
1361,79
1258,75
1169,17
1093,79
1051,79
1007,70
854,87
860,59
816,93

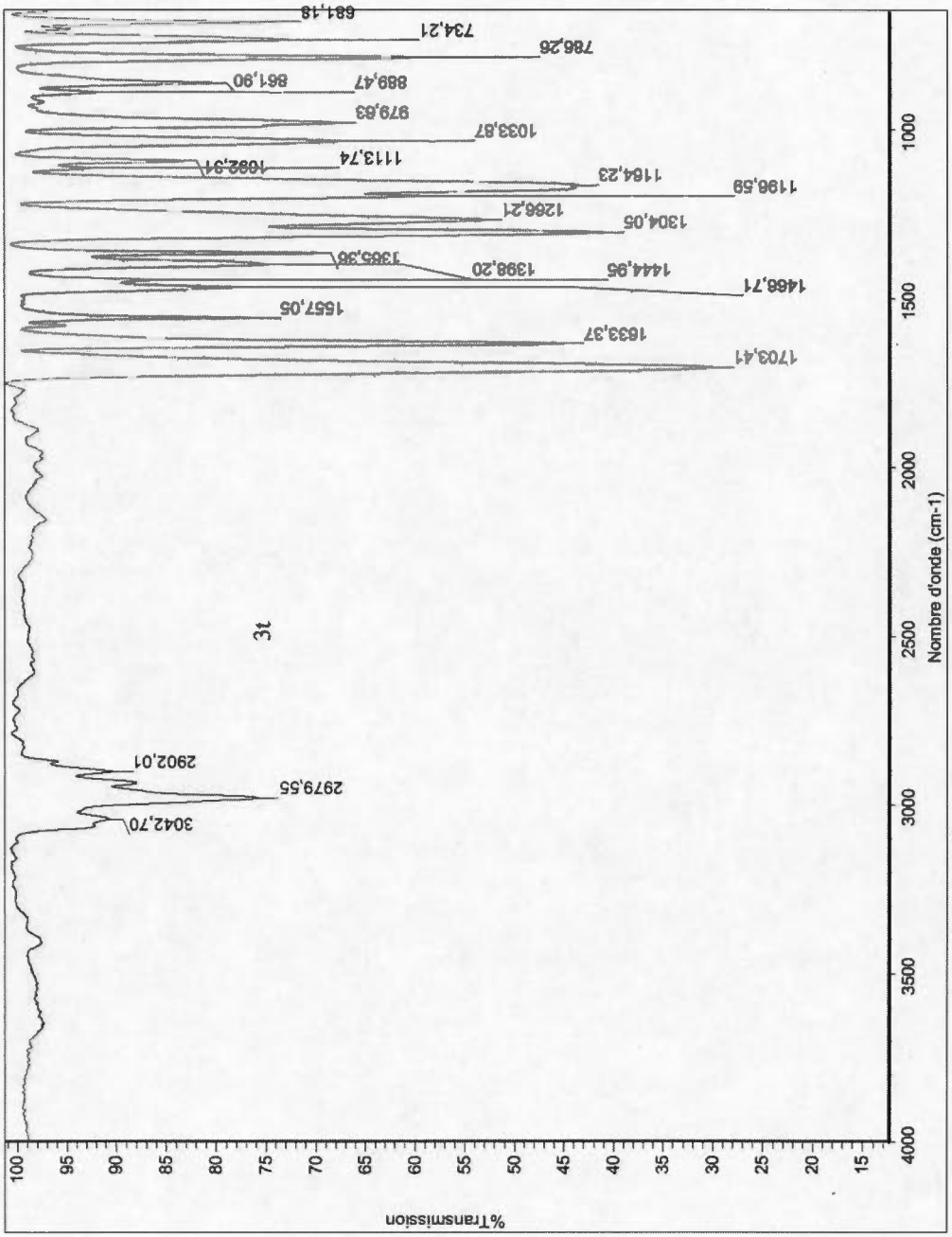

3s
f1 (ppm)

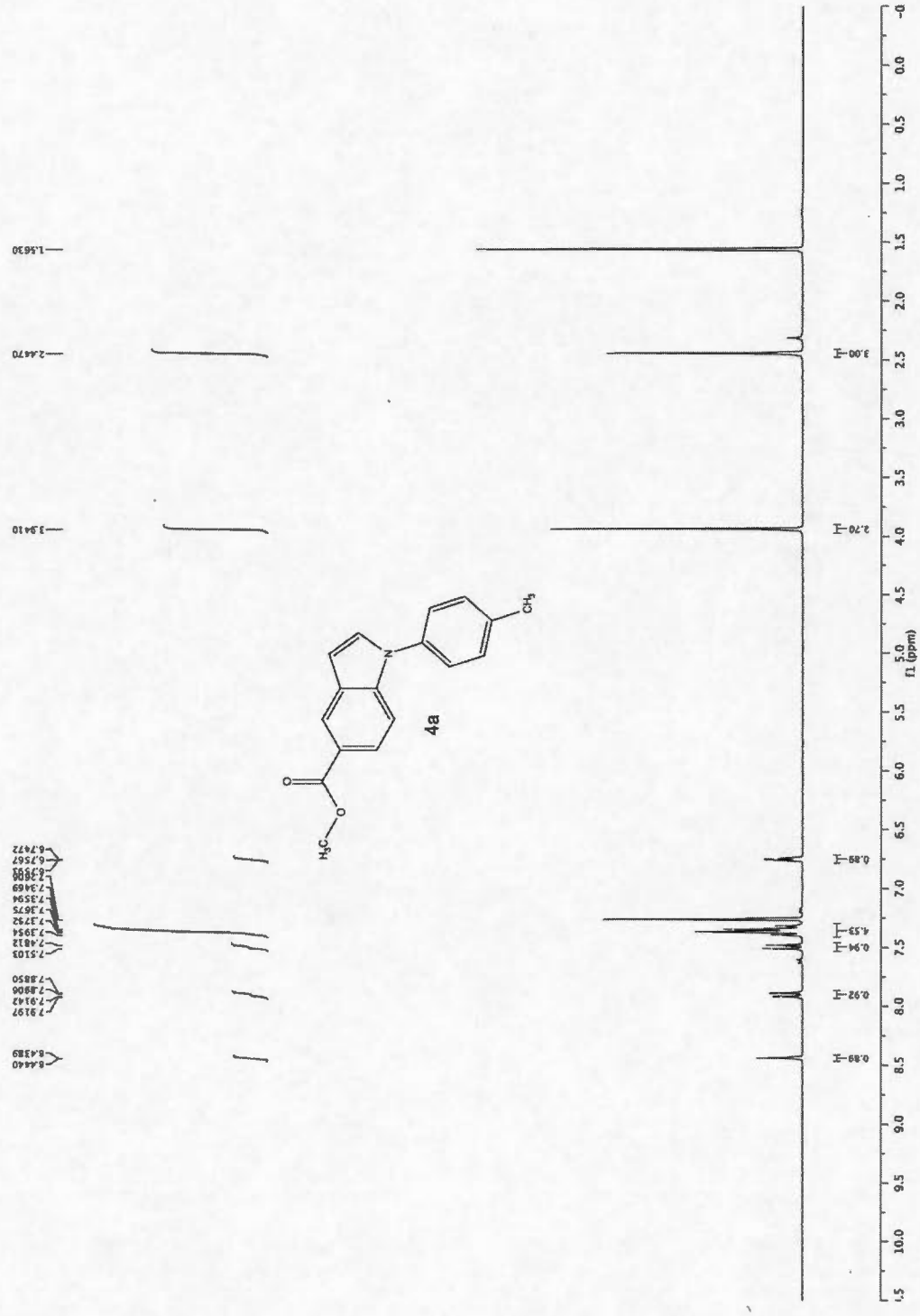

25.1376
70.3110
125.1259
130.4183
134.8492
136.8362
147.3942
155.5800
3s
OH
CH3
Bi
HO
f1 (ppm)


%Transmission
Nombre d'onde (cm-1)
3s
3348,85
3045,06
2971,59
2869,24
1583,88
1563,38
1447,39
1412,85
1387,95
1330,00
1264,23
1198,86
1108,74
1082,25
1059,74
1007,78
993,18
899,41
787,95
732,75
701,57

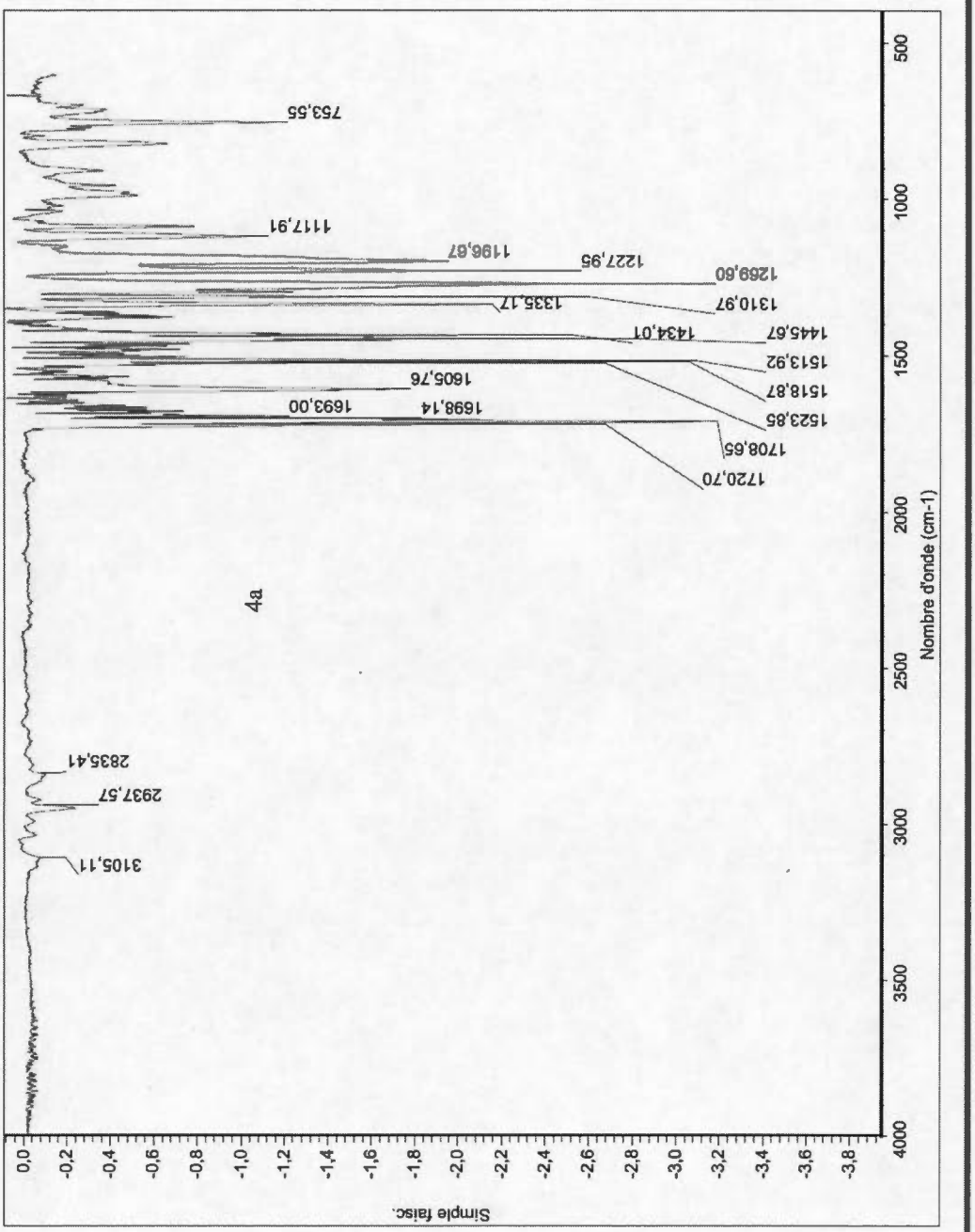
3t
f1 (ppm)


14.3943
60.5264
118.9562
127.5505
131.1745
136.5868
137.3010
139.3285
144.5020
156.0675
166.8292
3t
Bi
CH3
O
H3C
f1 (ppm)

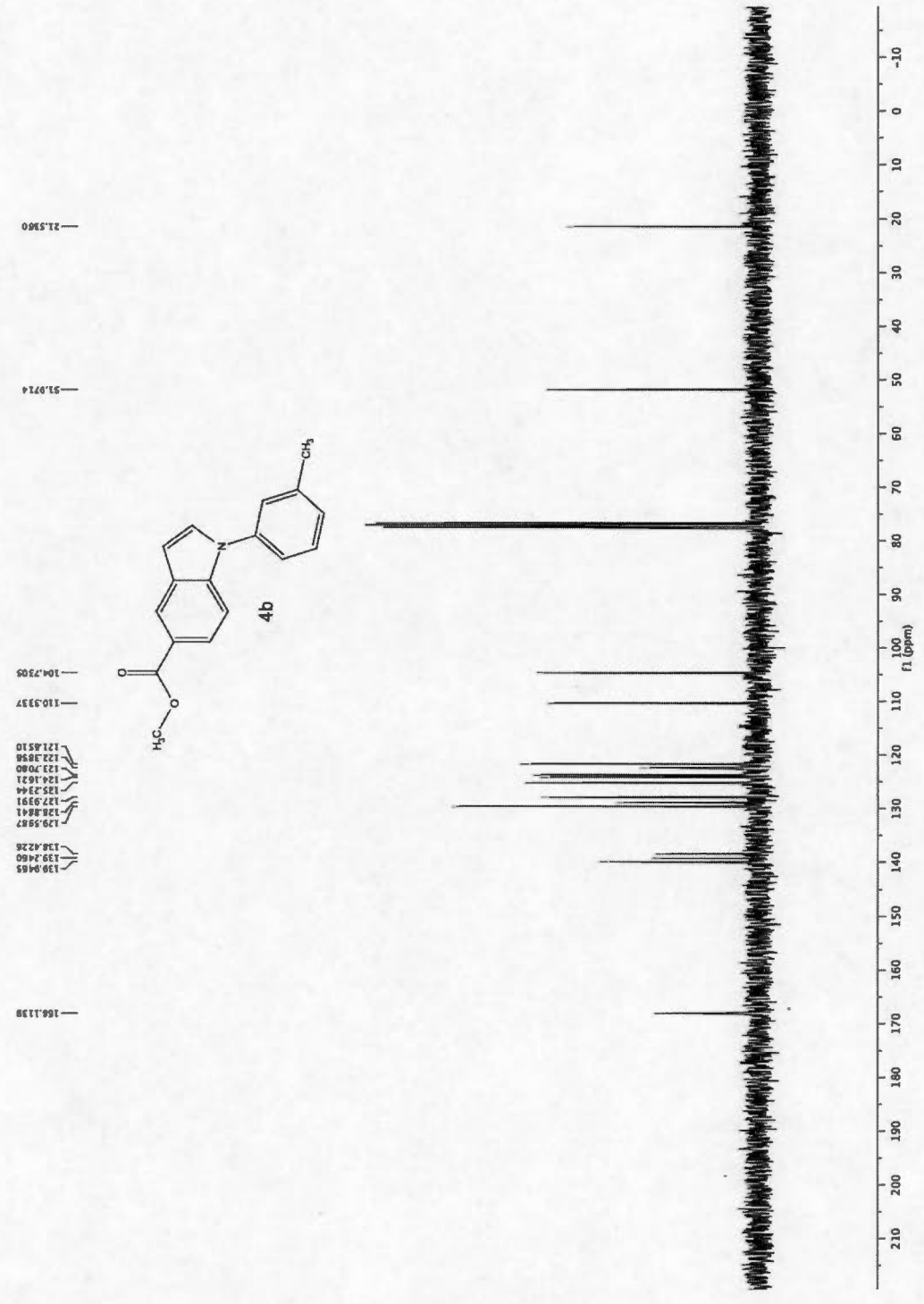

%Transmission
Nombre d'onde (cm-1)
3t
3042,70
2979,55
2902,01
1703,41
1633,37
1557,05
1466,71
1444,95
1398,20
1365,36
1304,05
1266,21
1196,59
1164,23
1113,74
1082,91
1033,87
979,63
889,47
861,90
786,26
734,21
681,18

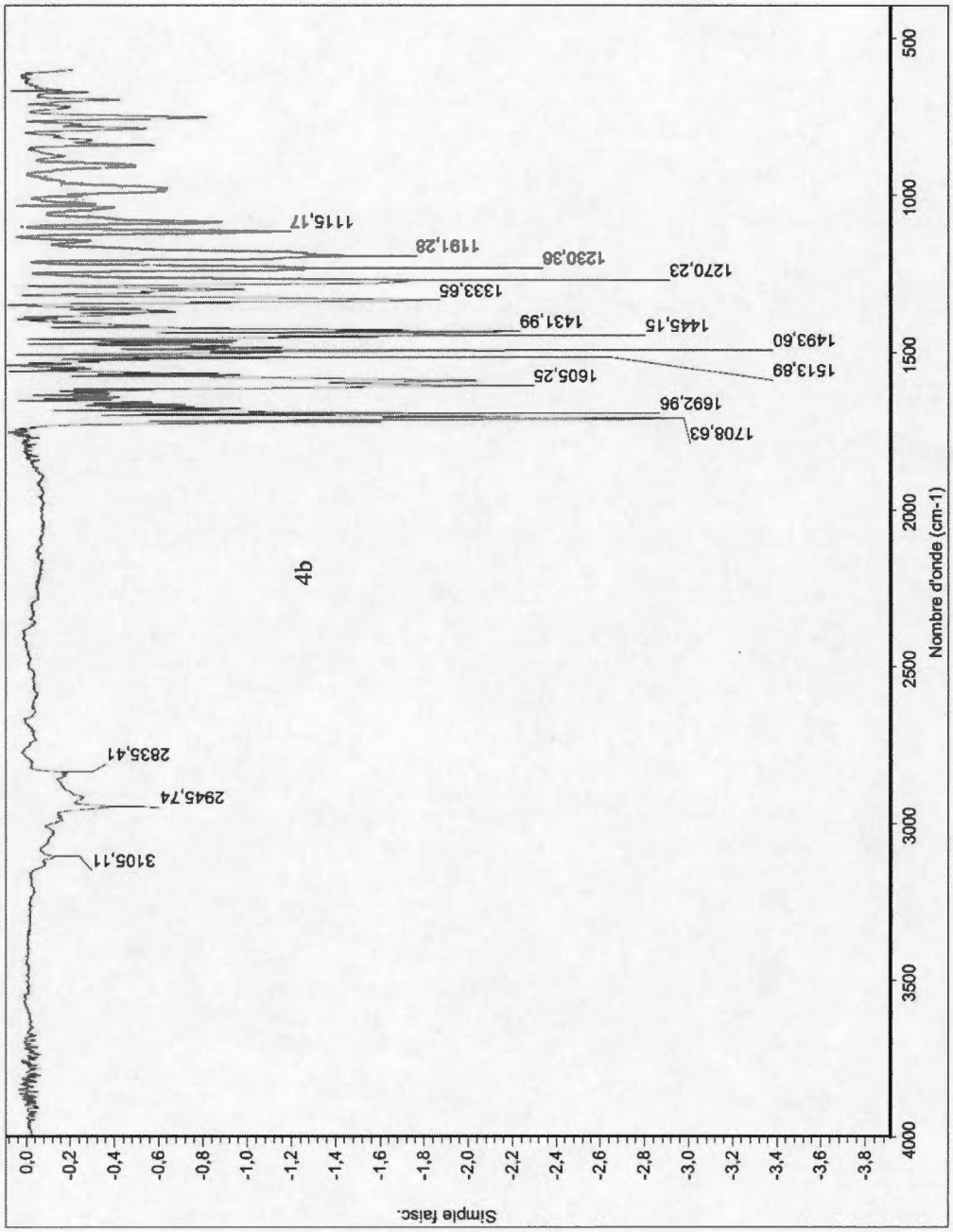

8.4460
8.4389
7.9197
7.9142
7.8806
7.8850
7.5103
7.4812
7.3954
7.3792
7.3675
7.3594
7.3469
7.2806
6.7503
6.7567
6.7472
3.9410
2.4470
1.5630
4a
f1 (ppm)

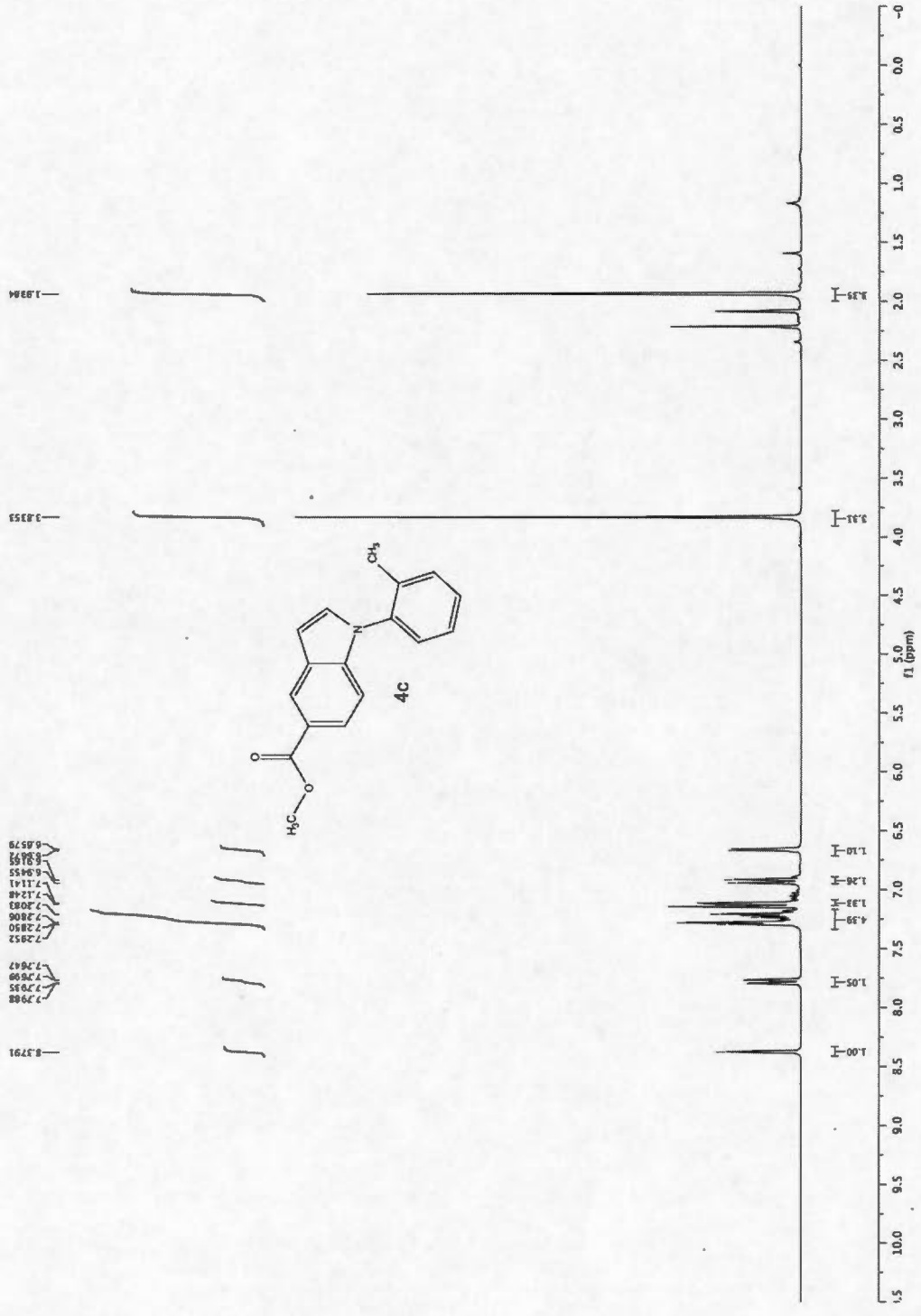
21.1710
51.8611
104.5926
110.2503
122.3188
123.6701
124.1560
128.2788
128.8531
130.3712
136.7728
137.1898
137.3092
138.5317
168.1256
4a
f1 (ppm)

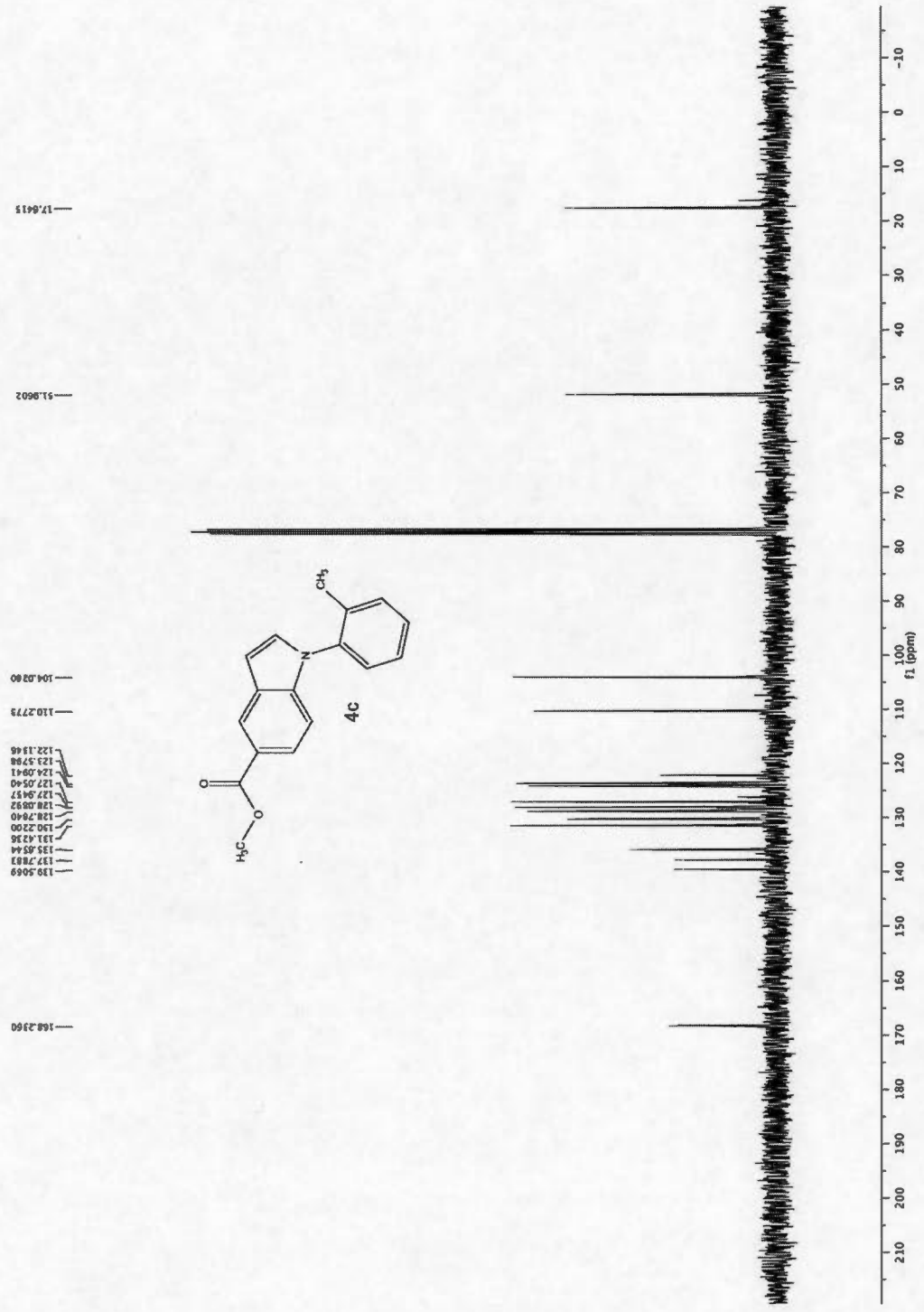

4a
Simple faisc.
Nombre d'onde (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
0,0
-0,2
-0,4
-0,6
-0,8
-1,0
-1,2
-1,4
-1,6
-1,8
-2,0
-2,2
-2,4
-2,6
-2,8
-3,0
-3,2
-3,4
-3,6
-3,8
3105,11
2937,57
2835,41
1720,70
1708,65
1693,00
1698,14
1605,76
1523,85
1518,87
1513,92
1445,67
1434,01
1335,17
1310,97
1269,60
1227,95
1196,67
1117,91
753,55

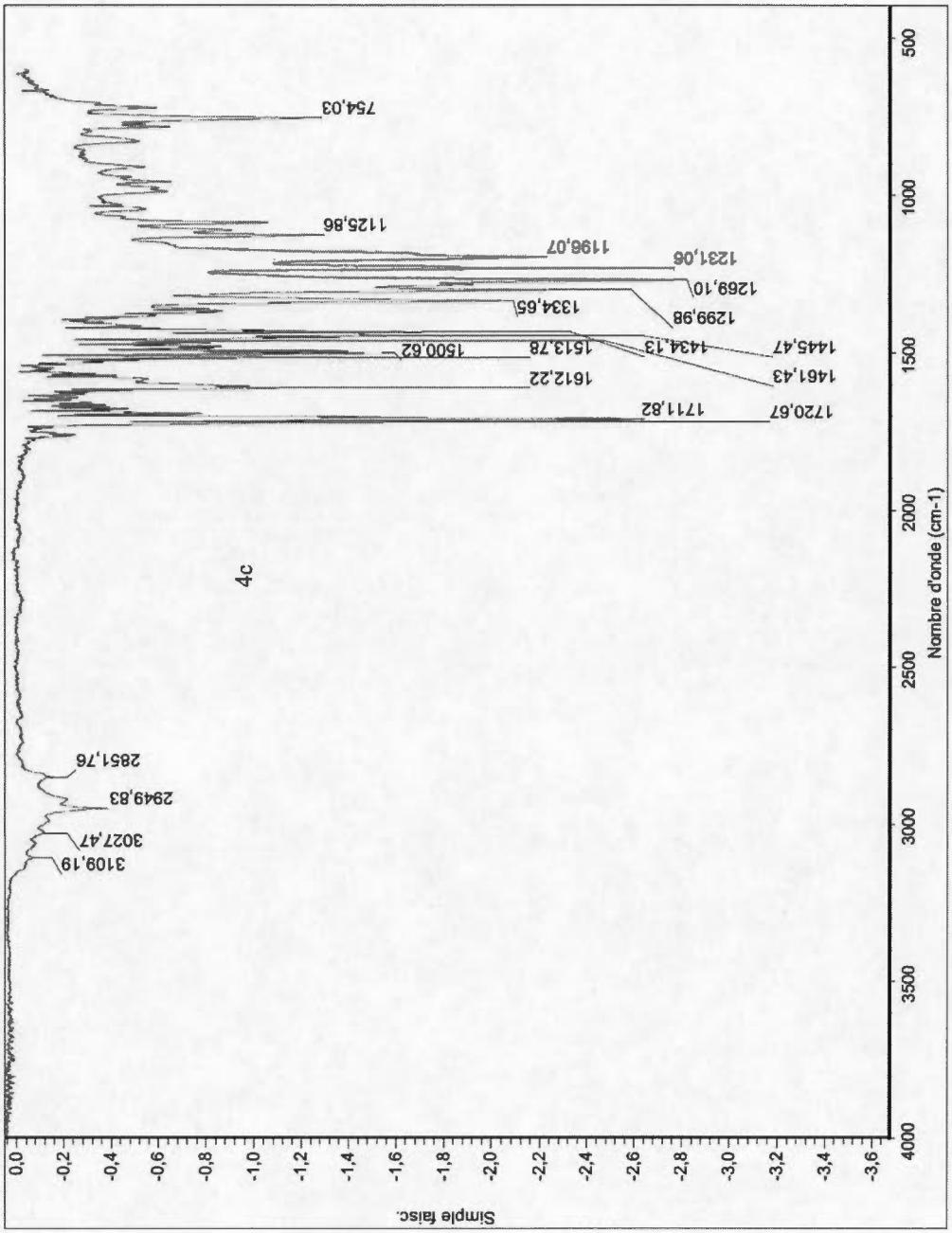
8.3516
7.8342
7.8246
7.8050
7.7987
7.4425
7.4131
7.3076
7.3046
7.2789
7.2721
7.2611
7.1925
6.6454
2.3457
3.8415
1.00
3.25
3.22
f1 (ppm)
4b

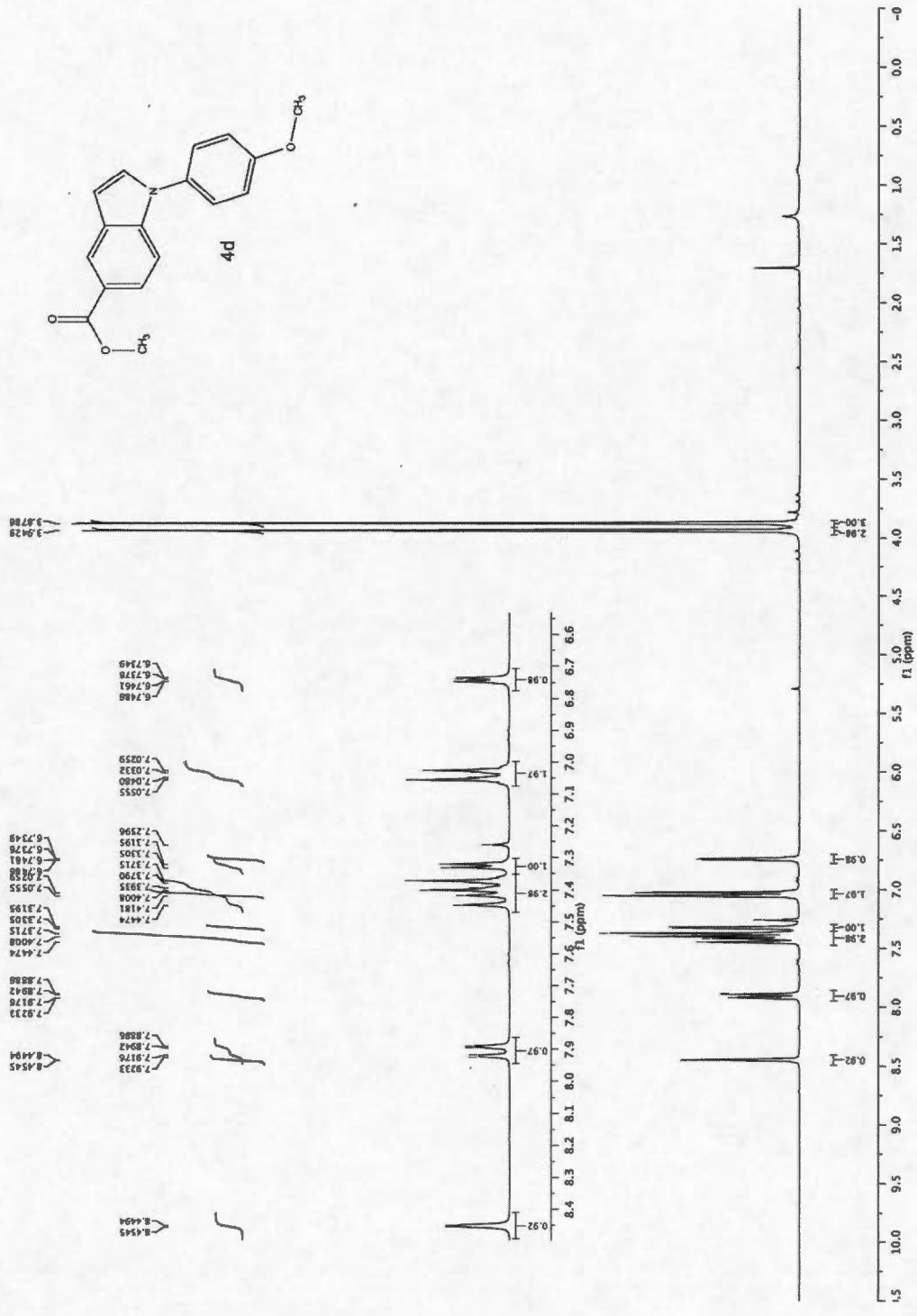

21.5360
51.9714
104.7305
110.3337
121.8510
122.2056
123.7060
124.1621
125.2344
127.9991
128.8841
129.5987
138.4226
139.2460
139.9465
166.1139
4b
f1 (ppm)

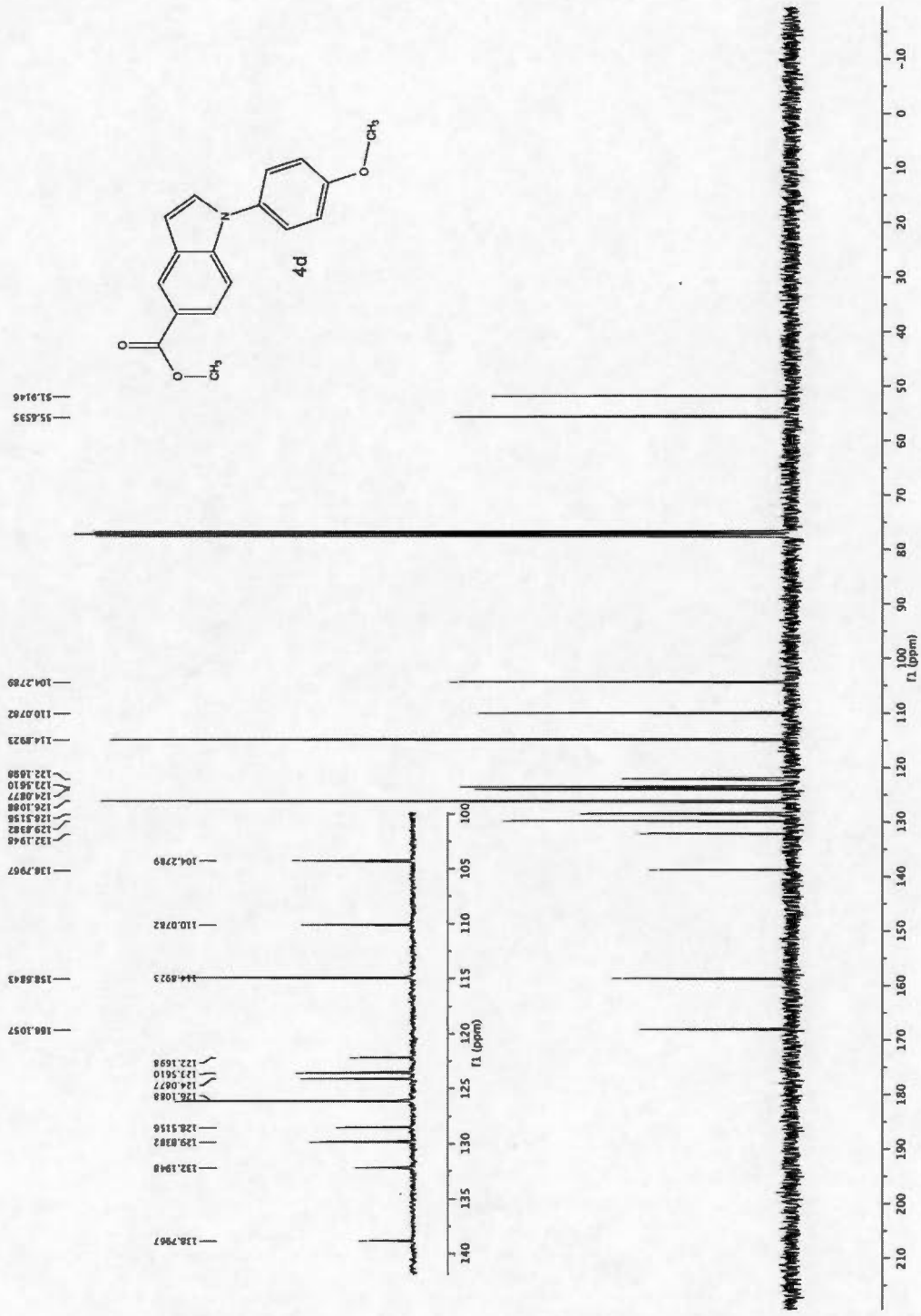

4b
Simple faisc.
Nombre d'onde (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
0,0
-0,2
-0,4
-0,6
-0,8
-1,0
-1,2
-1,4
-1,6
-1,8
-2,0
-2,2
-2,4
-2,6
-2,8
-3,0
-3,2
-3,4
-3,6
-3,8
3105,11
2945,74
2835,41
1708,63
1692,96
1605,25
1513,89
1493,60
1445,15
1431,99
1333,65
1270,23
1230,36
1191,28
1115,17

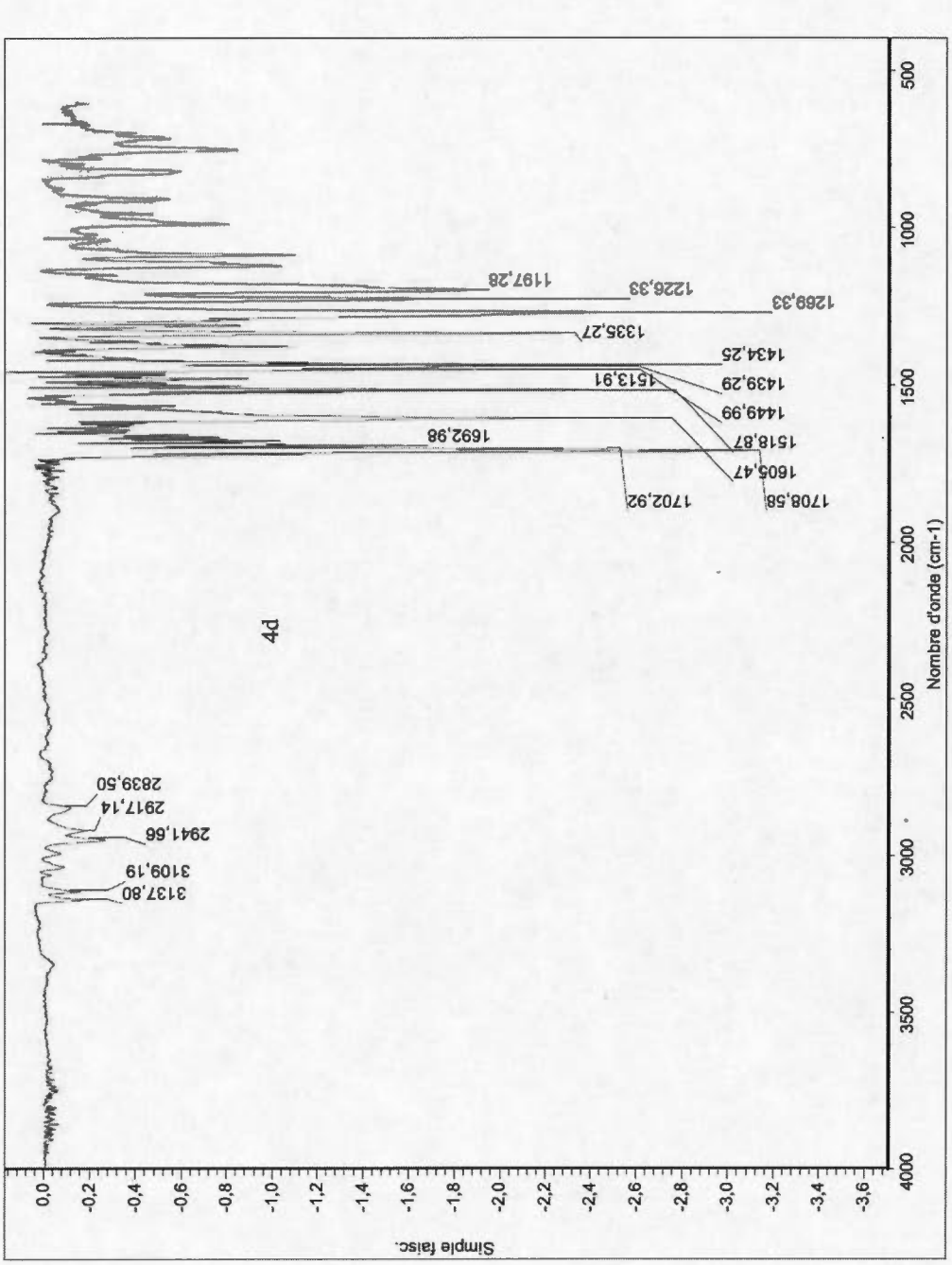

4c
f1 (ppm)

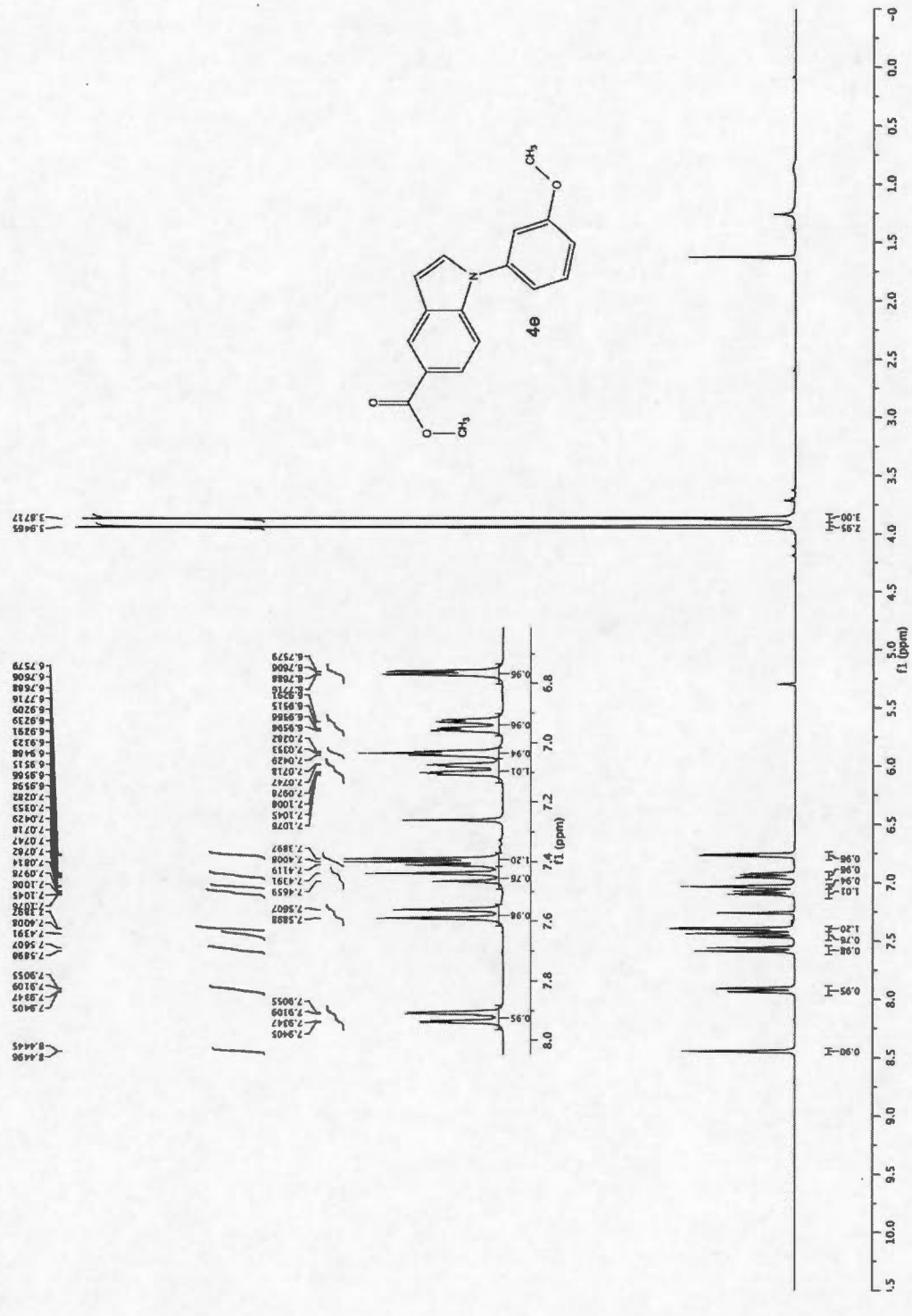

17.8615
51.8602
104.0280
110.2773
122.1346
123.5798
124.0941
127.0540
127.9457
128.0892
128.7940
130.2200
131.4236
135.8544
137.7883
139.5069
168.2360
4c
f1 (ppm)


4c
Simple faisc.
Nombre d'onde (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
0,0
-0,2
-0,4
-0,6
-0,8
-1,0
-1,2
-1,4
-1,6
-1,8
-2,0
-2,2
-2,4
-2,6
-2,8
-3,0
-3,2
-3,4
-3,6
3109,19
3027,47
2949,83
2851,76
1720,67
1711,82
1612,22
1513,78
1500,62
1461,43
1445,47
1434,13
1334,65
1299,98
1269,10
1231,06
1196,07
1125,86
754,03

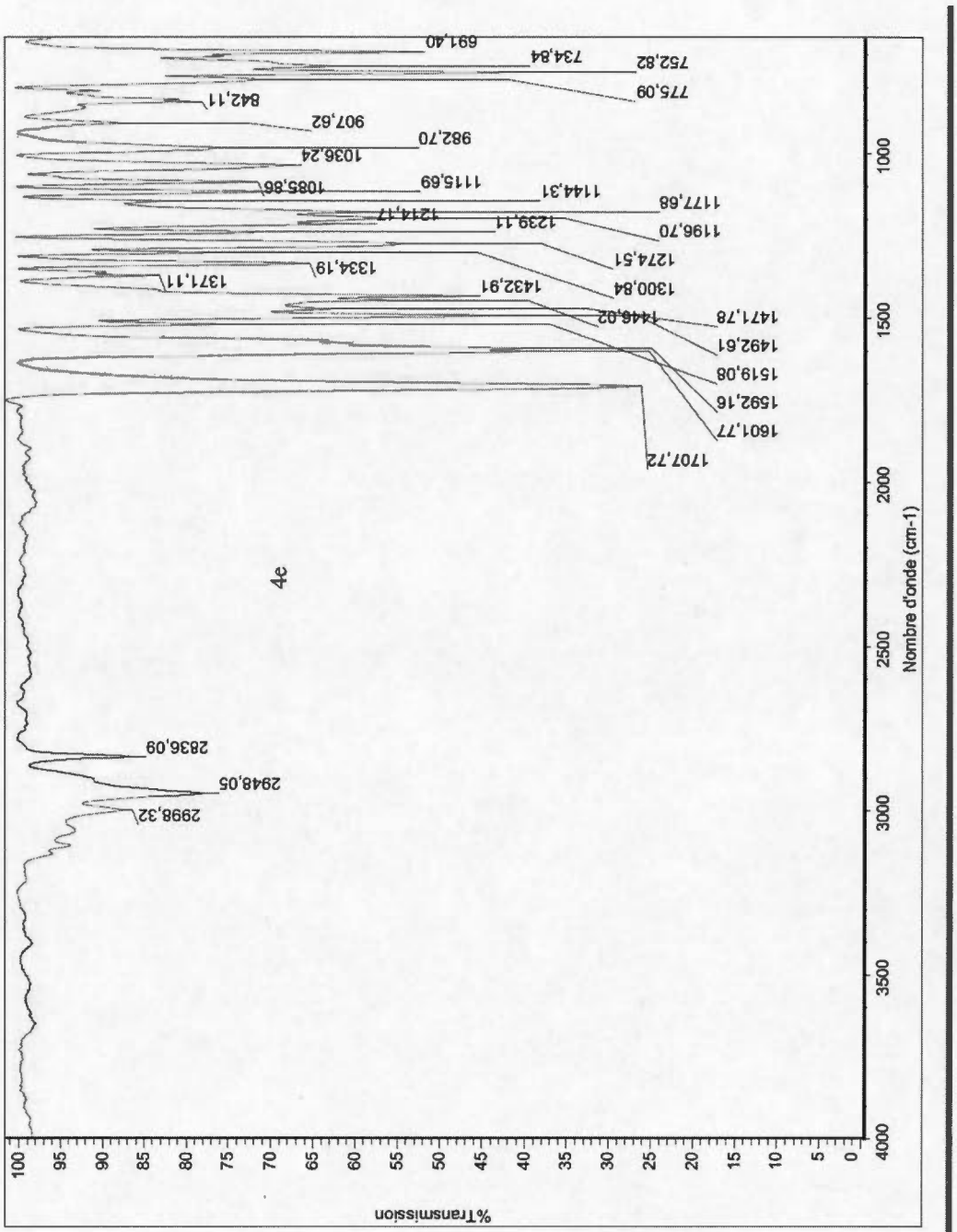

4d
f1 (ppm)

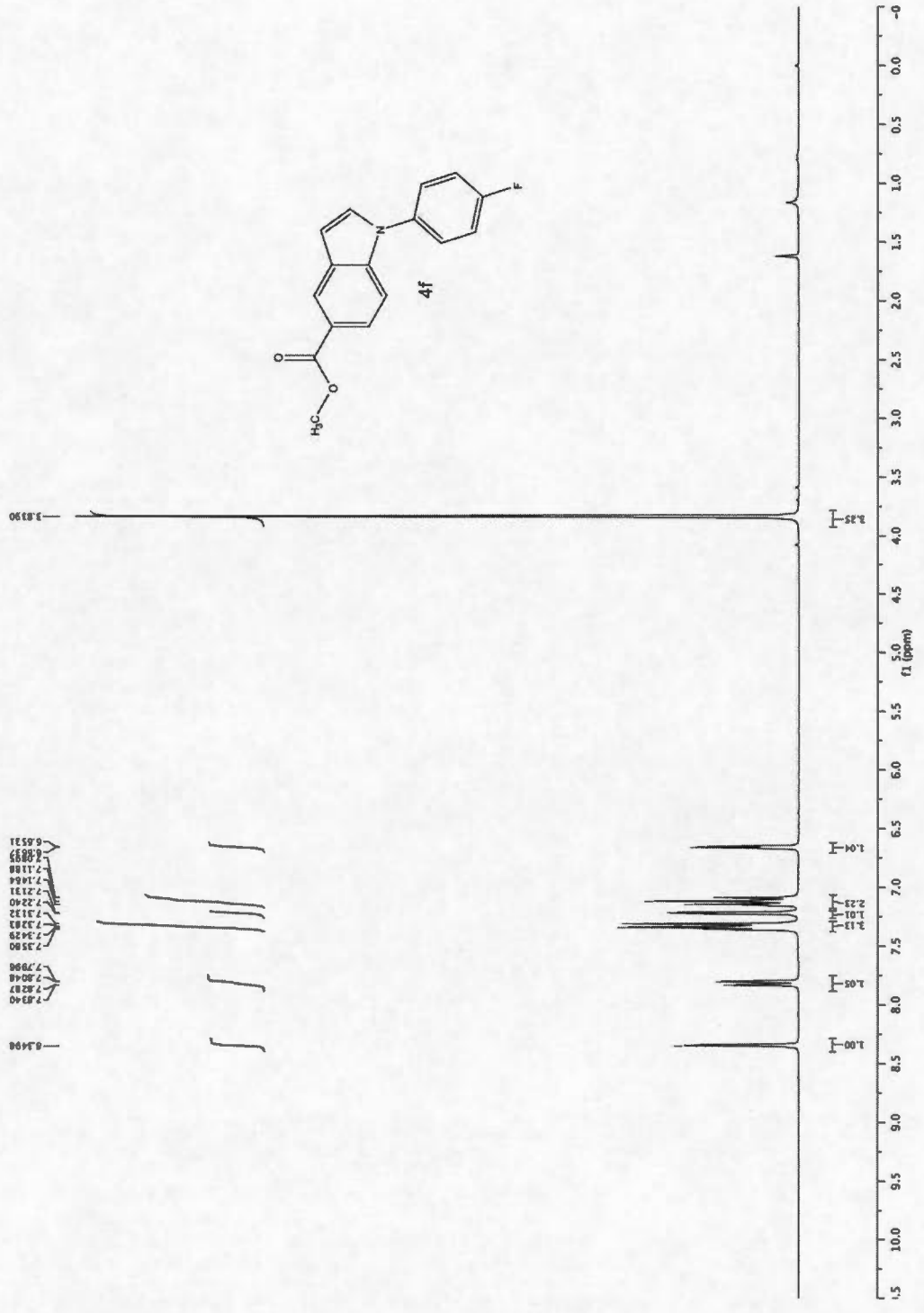

4d
51.9146
55.4535
104.2789
110.0762
114.8923
122.1698
123.3610
124.0677
126.1088
128.3156
129.8382
132.1948
138.7967
158.8643
166.1057
f1 (ppm)

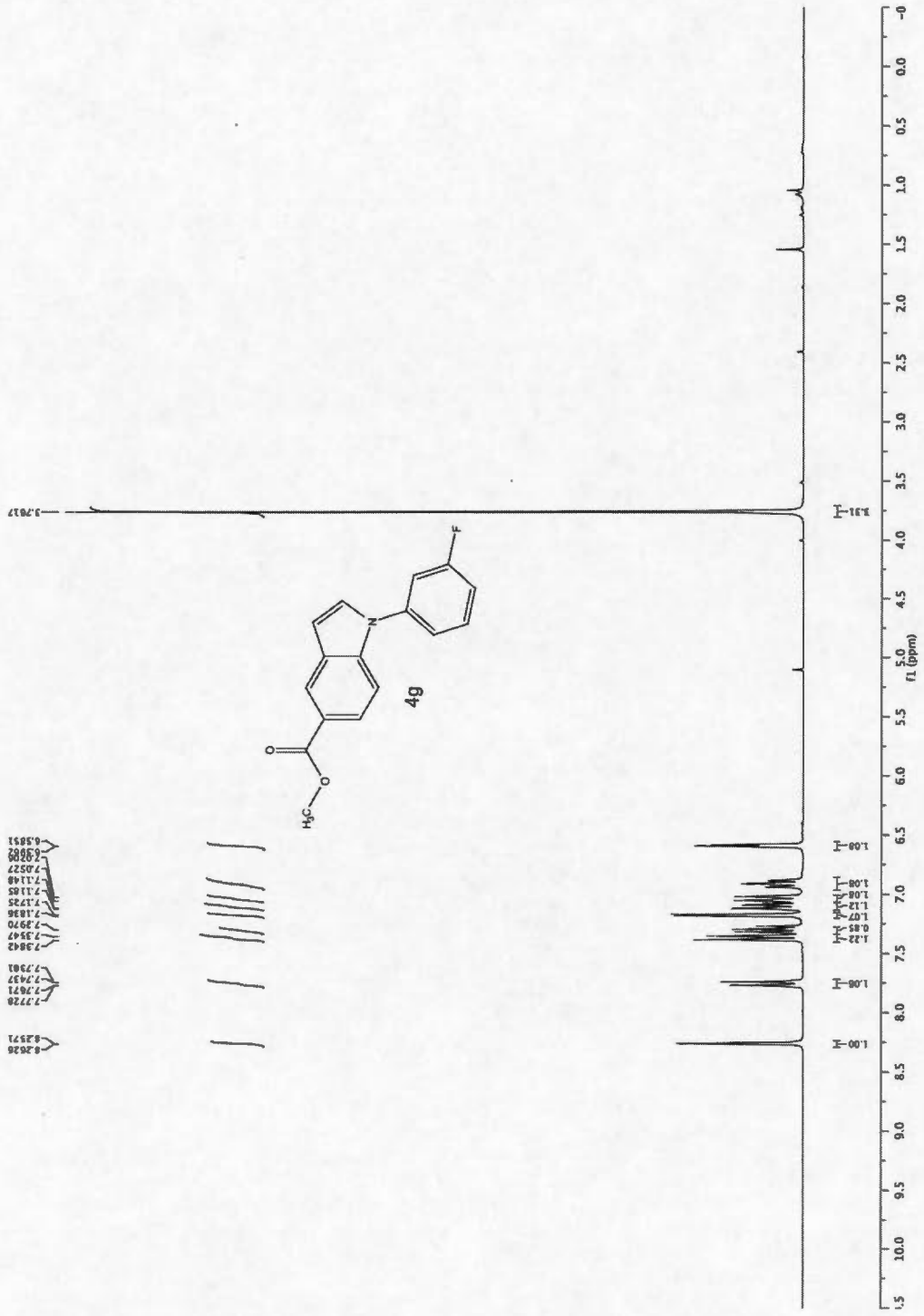

4d
Simple faisc.
Nombre d'onde (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
0,0
-0,2
-0,4
-0,6
-0,8
-1,0
-1,2
-1,4
-1,6
-1,8
-2,0
-2,2
-2,4
-2,6
-2,8
-3,0
-3,2
-3,4
-3,6
3137,80
3109,19
2941,66
2917,14
2839,50
1708,58
1605,47
1518,87
1449,99
1439,29
1434,25
1335,27
1268,33
1226,33
1197,28
1513,91
1702,92
1692,98

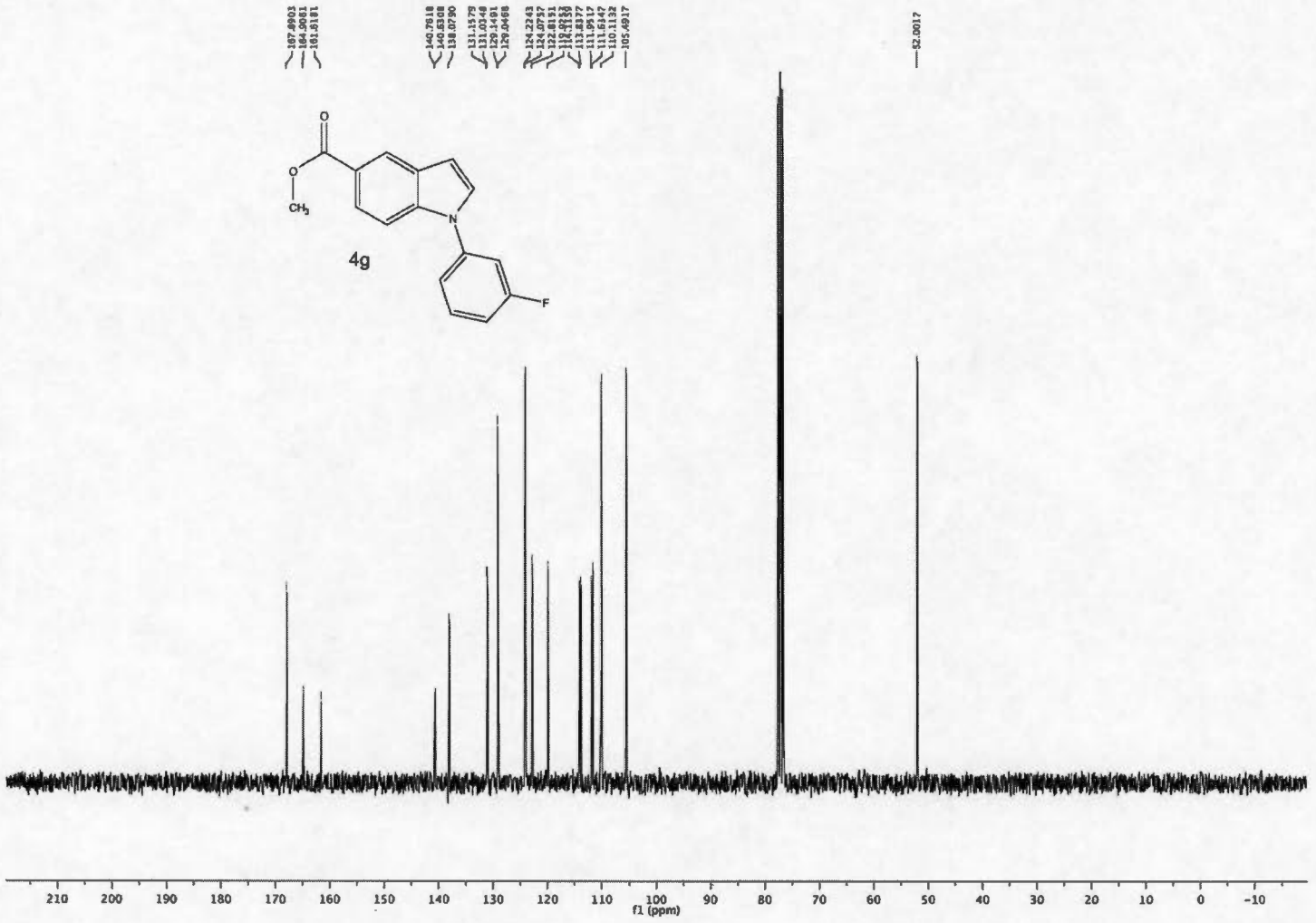

4e
f1 (ppm)

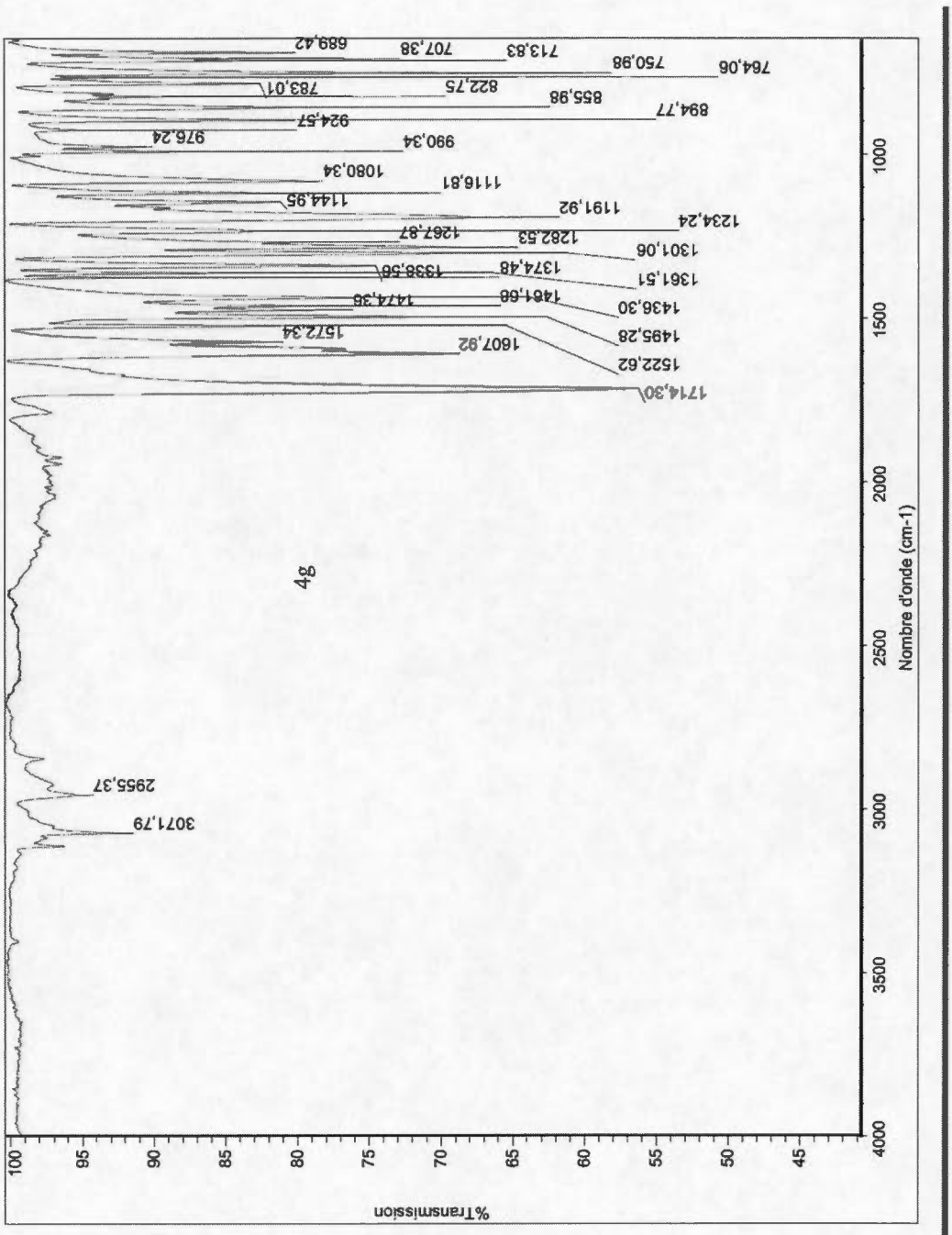
168.0285
160.4634
140.3650
138.2896
130.5441
129.4555
128.8093
124.1291
123.7615
122.4517
116.7268
112.5471
110.4926
110.3407
104.8583
55.3804
51.8973
4e
f1 (ppm)

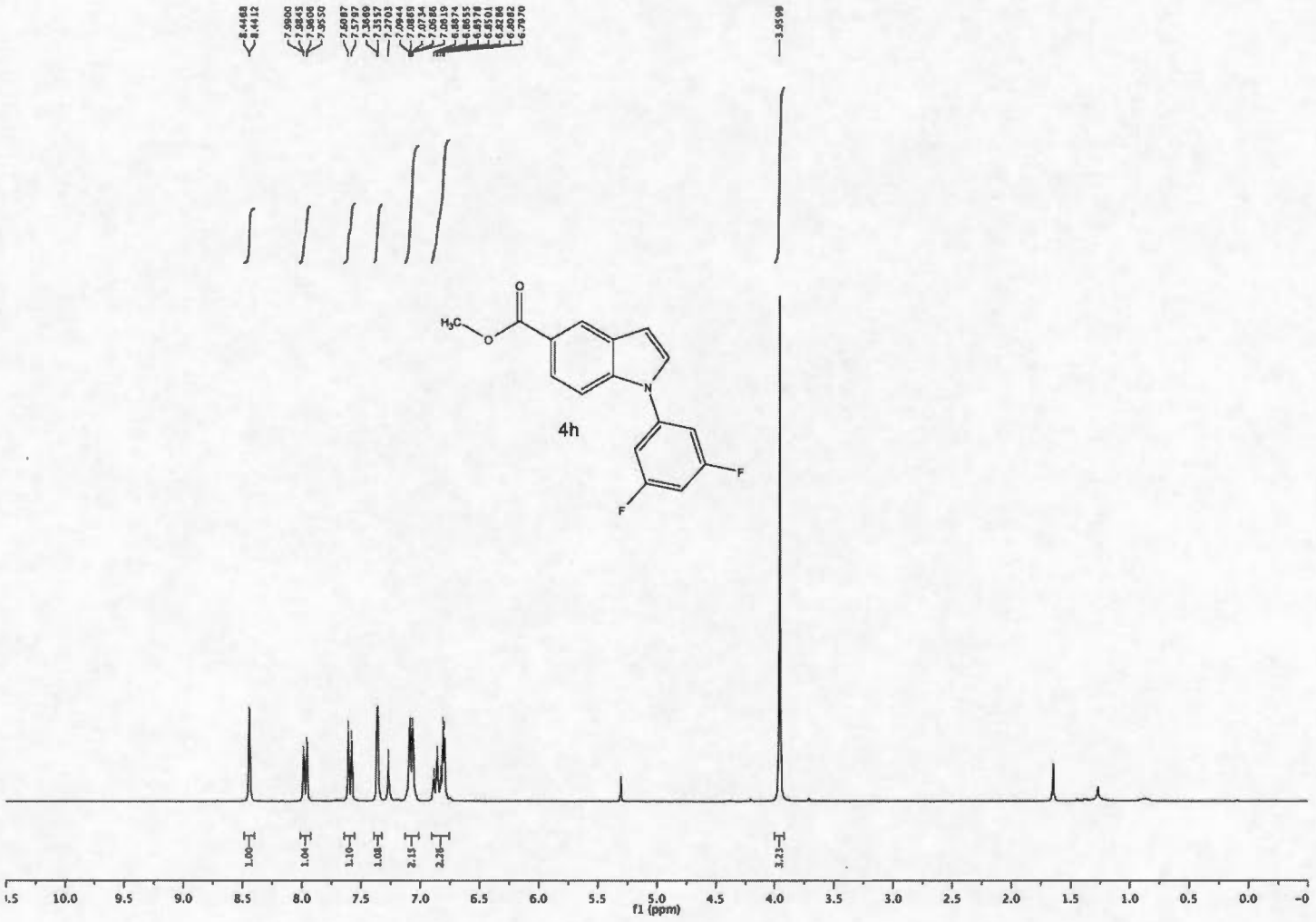

4e
%Transmission
Nombre d'onde (cm-1)
4000
3500
3000
2500
2000
1500
1000
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
2998,32
2948,05
2836,09
1707,72
1601,77
1592,16
1519,08
1492,61
1471,78
1446,02
1432,91
1371,11
1334,19
1300,84
1274,51
1239,11
1214,17
1196,70
1177,68
1144,31
1115,69
1085,86
1036,24
982,70
907,62
842,11
775,09
752,82
734,84
691,40

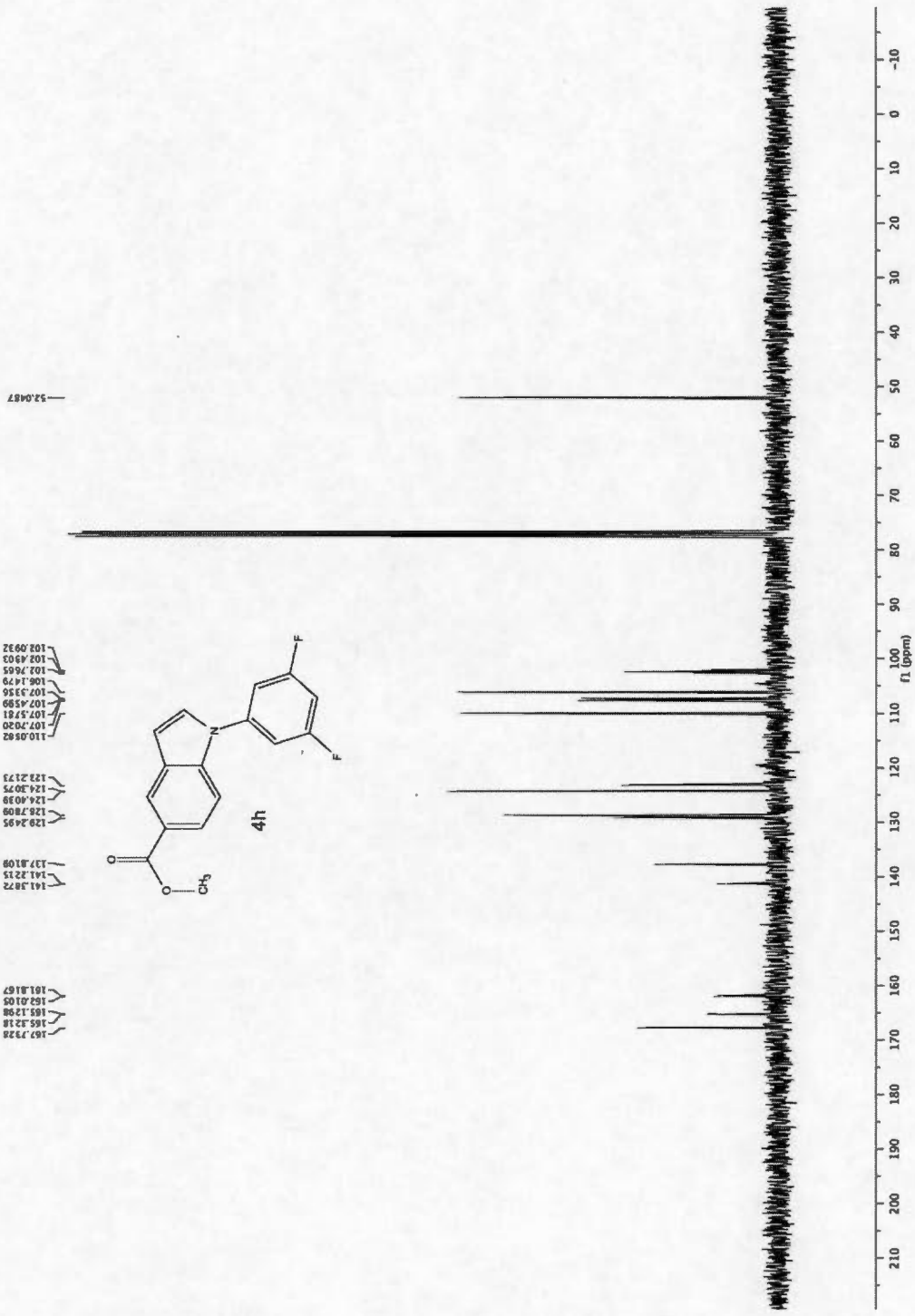

4f
F
N
O
O
H3C
f1 (ppm)

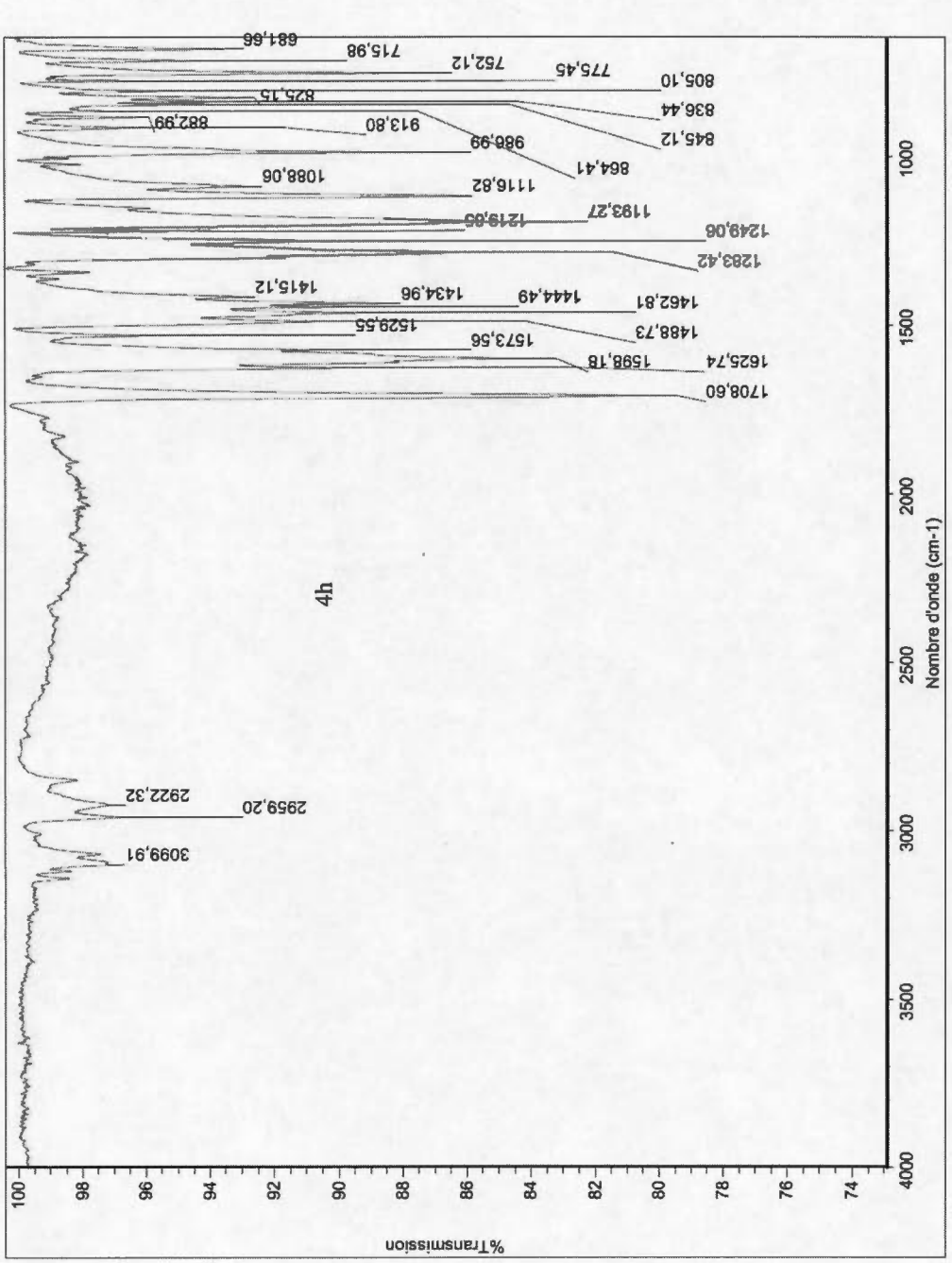

4g
F
N
O
O
H3C
f1 (ppm)

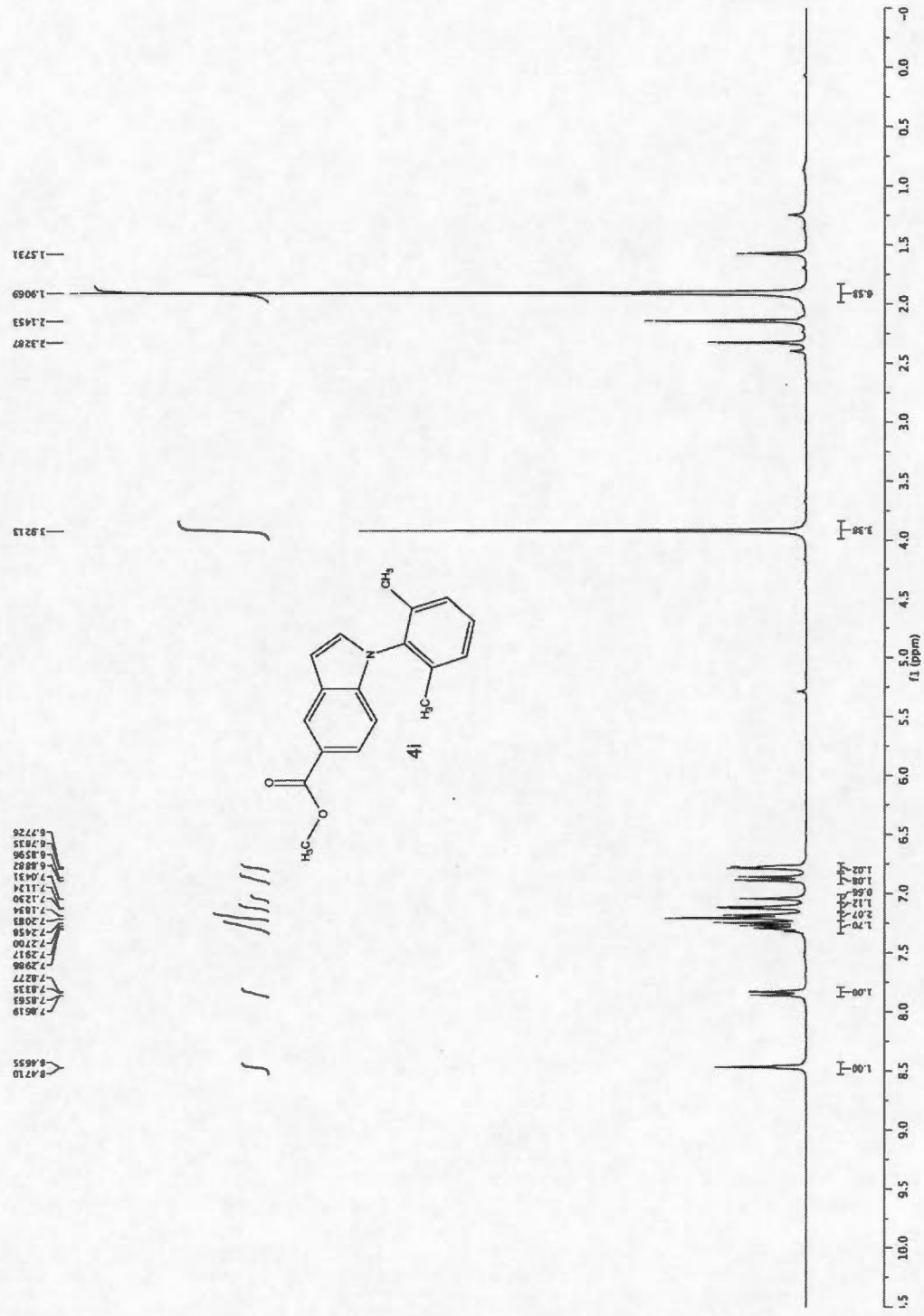

167.4903
164.9061
161.6181
140.7618
140.6308
138.0790
131.1573
131.0344
129.1491
129.0468
124.2243
124.0757
122.8111
122.7933
114.7158
113.8377
111.9917
111.6442
110.1132
105.4917
52.0017
O
O
CH3
N
F
4g
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

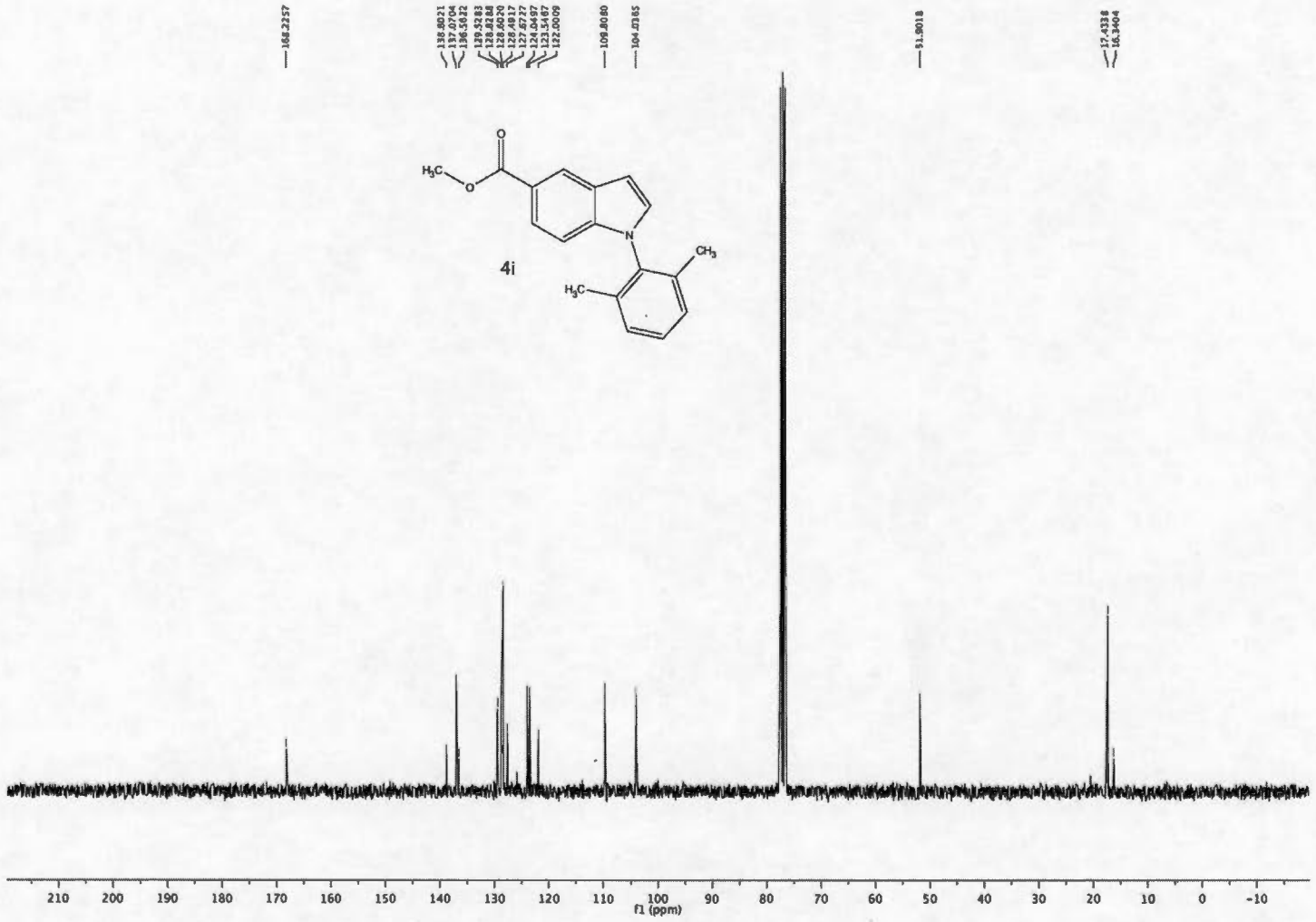

%Transmission
100
95
90
85
80
75
70
65
60
55
50
45
4000
3500
3000
2500
2000
1500
1000
Nombre d'onde (cm-1)
4g
3071,79
2955,37
1714,30
1607,92
1572,34
1522,62
1495,28
1474,38
1461,66
1436,30
1374,48
1361,51
1338,56
1301,06
1282,53
1267,87
1234,24
1191,92
1144,95
1116,81
1080,34
990,34
976,24
924,57
894,77
855,98
822,75
783,01
764,06
750,98
713,83
707,38
689,42

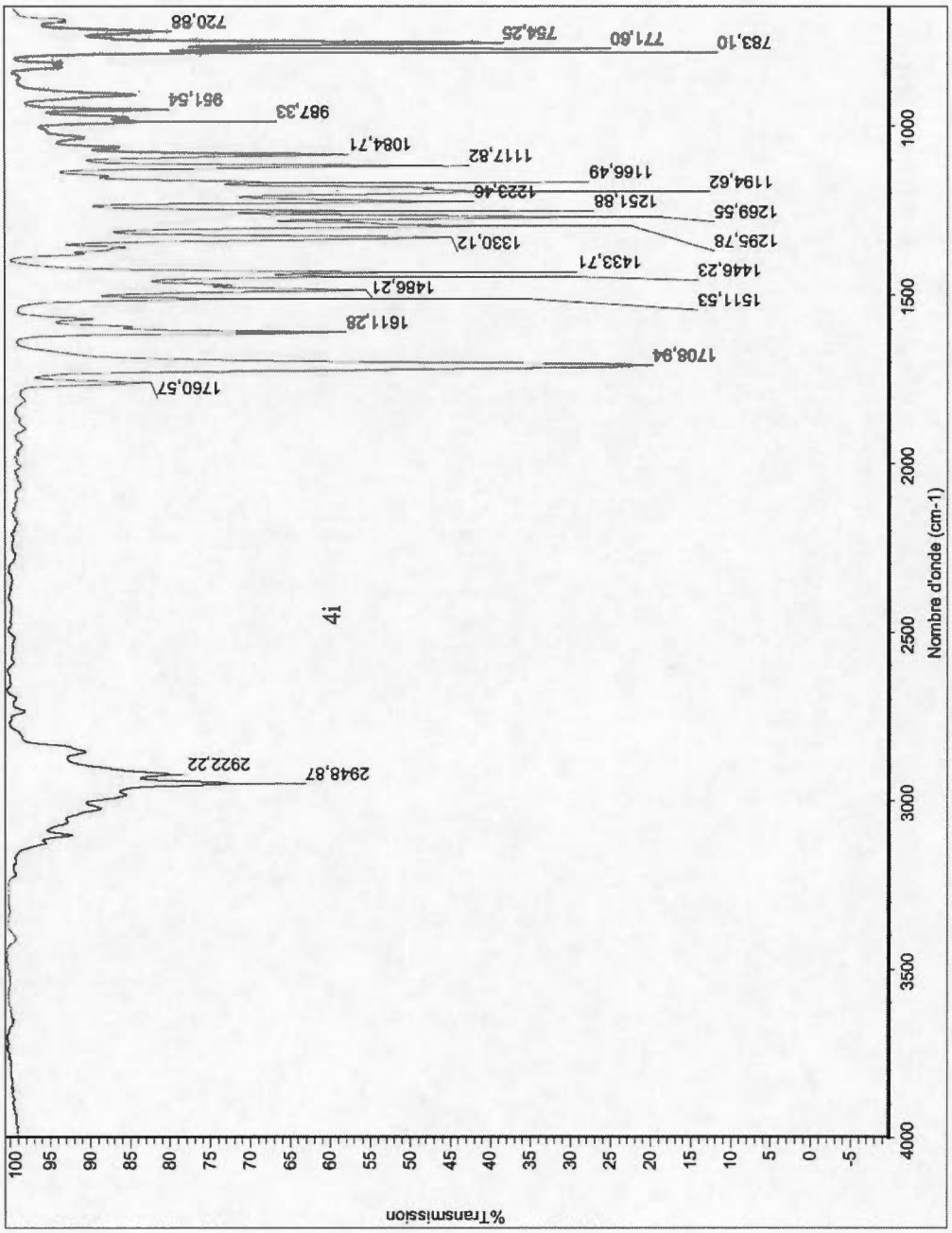

8.4468
8.4412
7.9800
7.9645
7.9588
7.9550
7.5087
7.5797
7.3669
7.3557
7.3703
7.3664
7.0681
7.0734
7.0686
7.0619
6.8874
6.8855
6.8578
6.8701
6.8701
6.8682
6.7970
3.9599
4h
F
F
1.00
1.04
1.10
1.08
2.15
2.26
3.23
f1 (ppm)

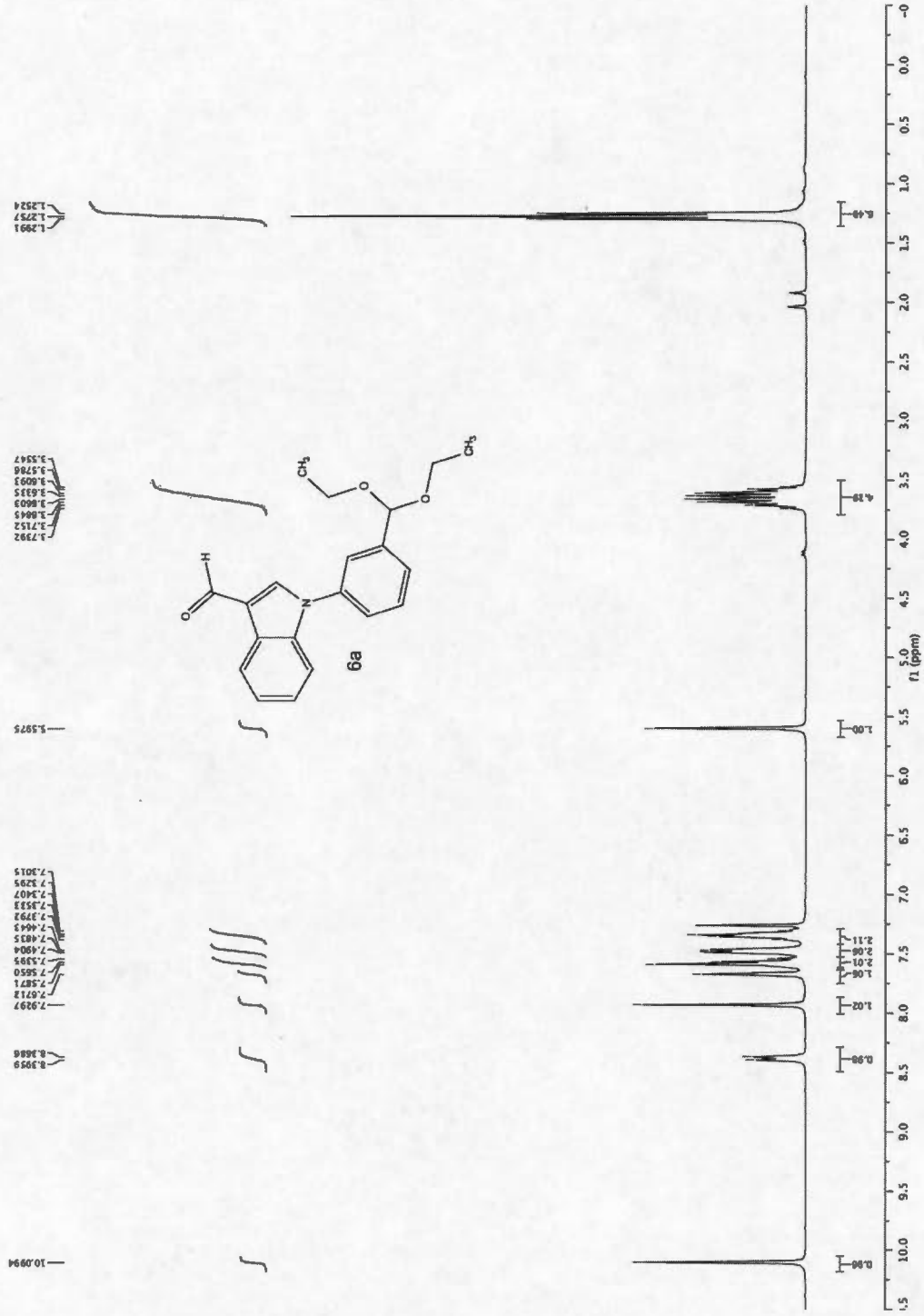

52.0487
110.0582
107.7020
107.5781
107.4599
107.3356
106.1479
102.7665
102.4903
102.0932
161.8167
162.7328
165.1298
165.3218
162.0105
161.3872
141.3215
137.8109
129.3495
128.7809
124.4039
124.3075
123.2173
4h
F
F
O
O
CH3
f1 (ppm)

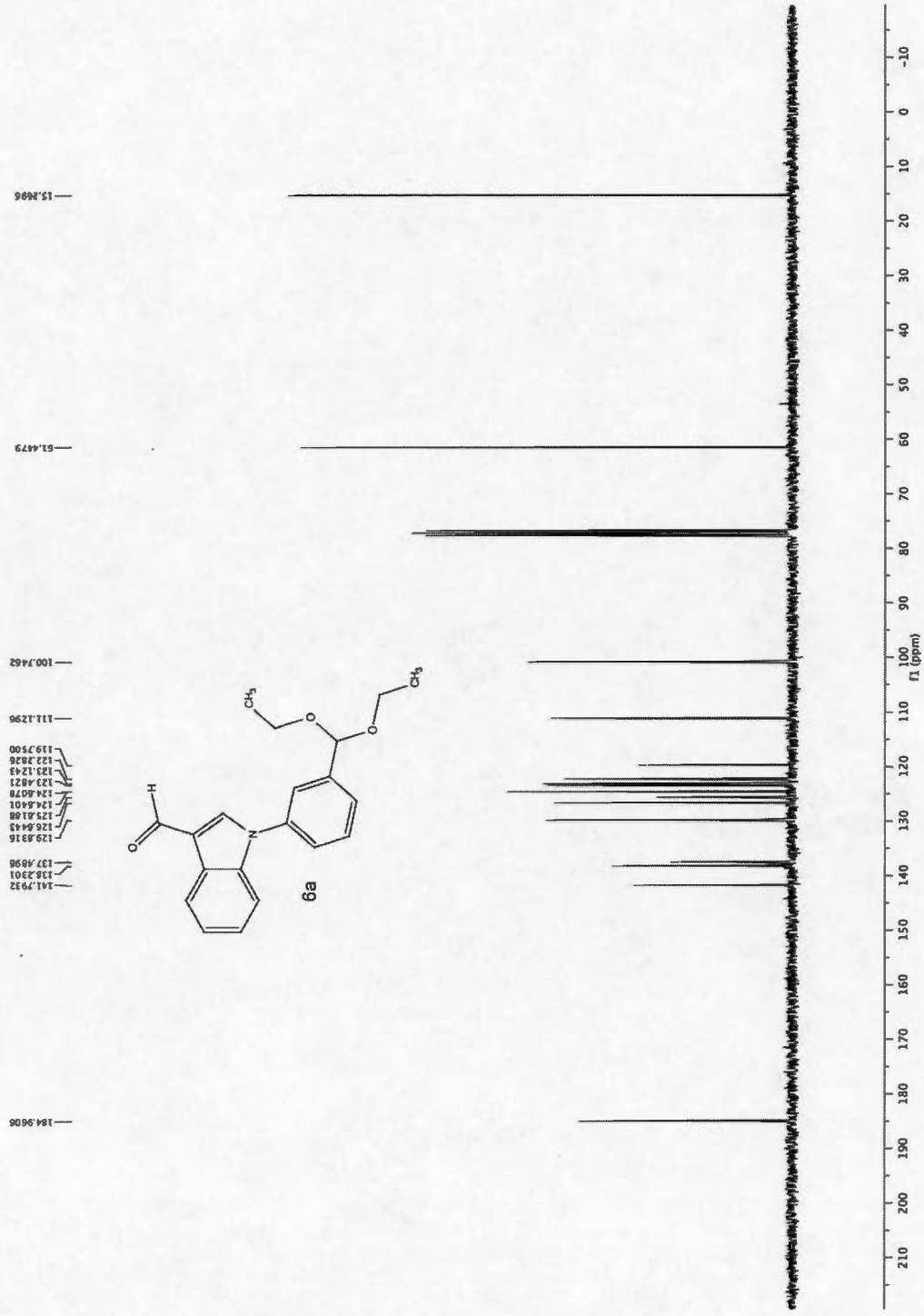

4h
%Transmission
Nombre d'onde (cm-1)
100
98
96
94
92
90
88
86
84
82
80
78
76
74
4000
3500
3000
2500
2000
1500
1000
3099,91
2959,20
2922,32
1708,60
1625,74
1598,18
1573,56
1529,55
1488,73
1462,81
1444,49
1434,96
1415,12
1283,42
1249,06
1219,05
1193,27
1116,82
1088,06
986,99
913,80
882,99
864,41
845,12
836,44
825,15
805,10
775,45
752,12
715,98
681,66

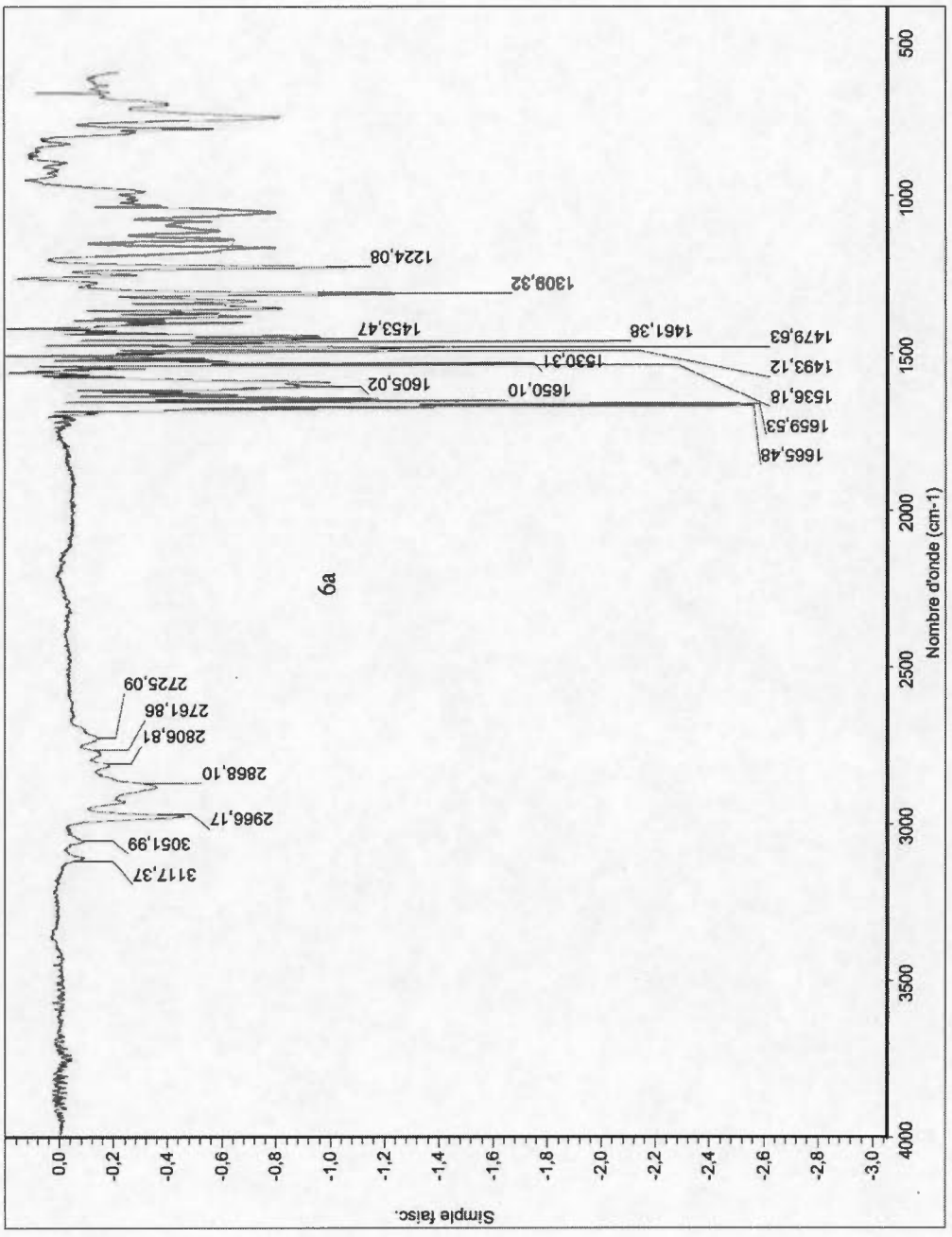

4i
f1 (ppm)

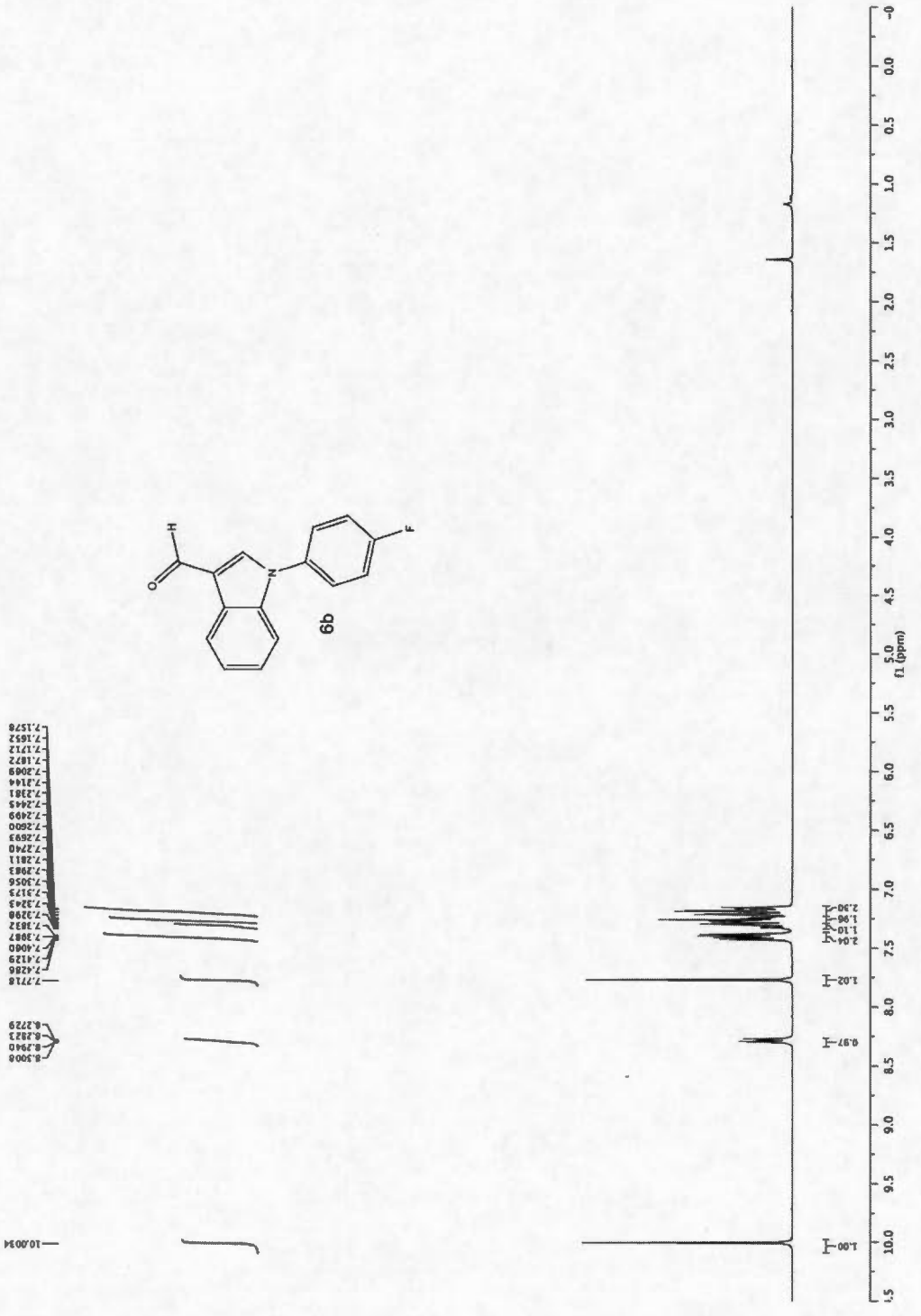

168.2257
138.8021
137.0704
136.5612
129.5283
128.8238
128.4630
128.4011
127.6717
124.0497
123.5467
122.0009
109.8080
104.4765
51.8018
17.4338
16.3404
4i
O
H3C
O
N
CH3
H3C
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

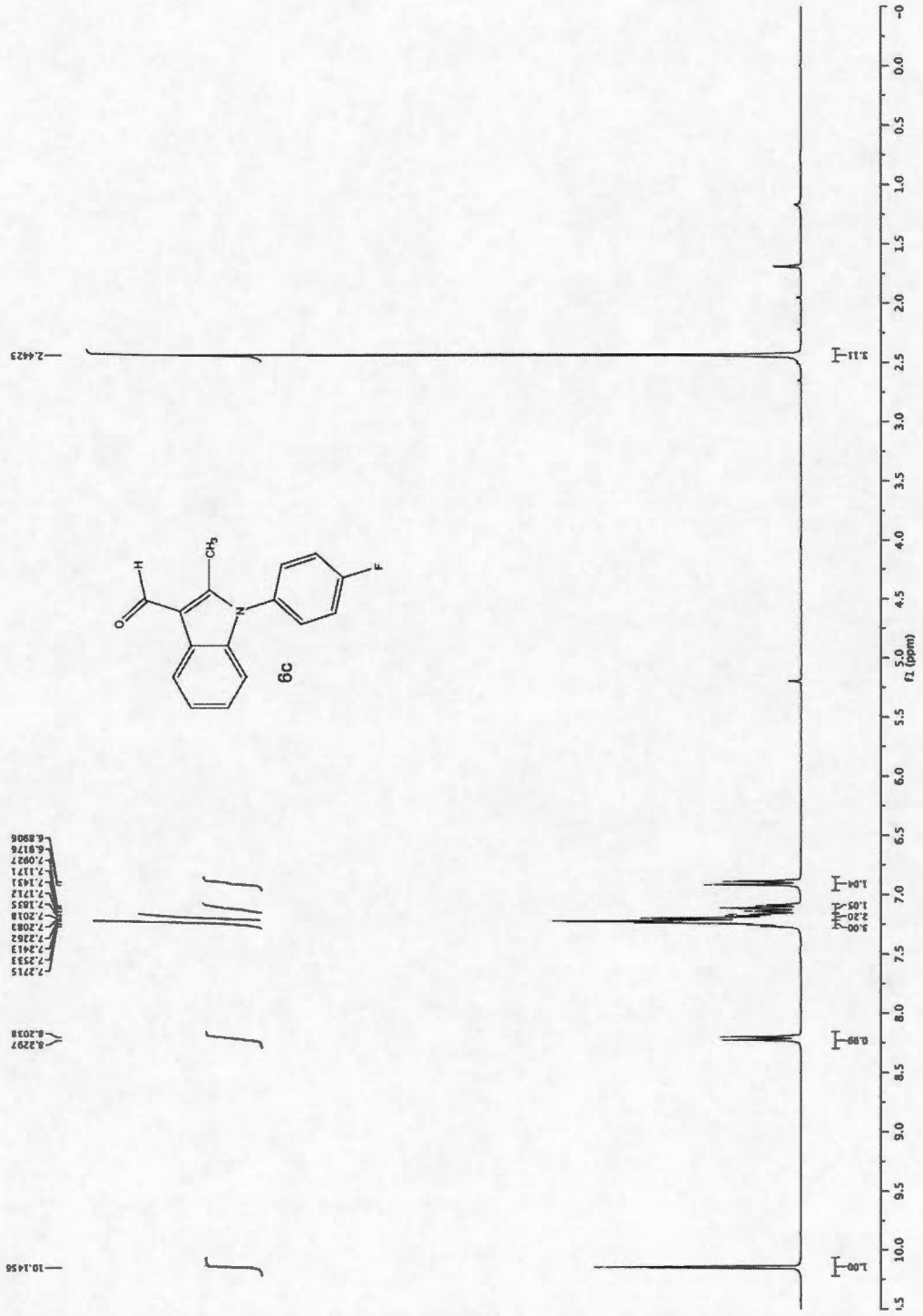

%Transmission
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
4000
3500
3000
2500
2000
1500
1000
Nombre d'onde (cm-1)
4i
2948,87
2922,22
1760,57
1708,94
1611,28
1511,53
1486,21
1446,23
1433,71
1330,12
1295,78
1269,55
1251,88
1223,46
1194,62
1166,49
1117,82
1084,71
987,33
951,54
783,10
771,80
754,25
720,88

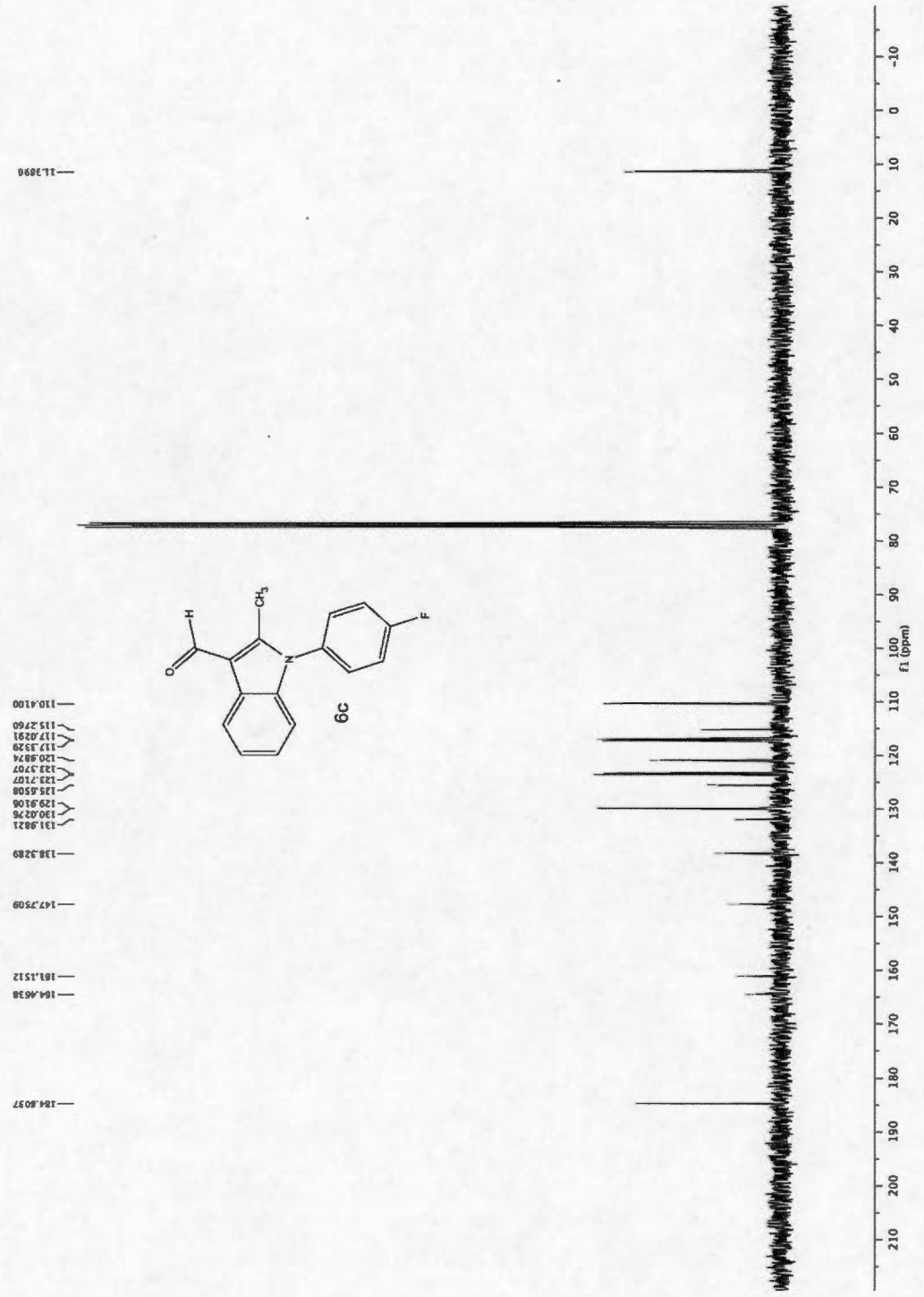

6a
f1 (ppm)

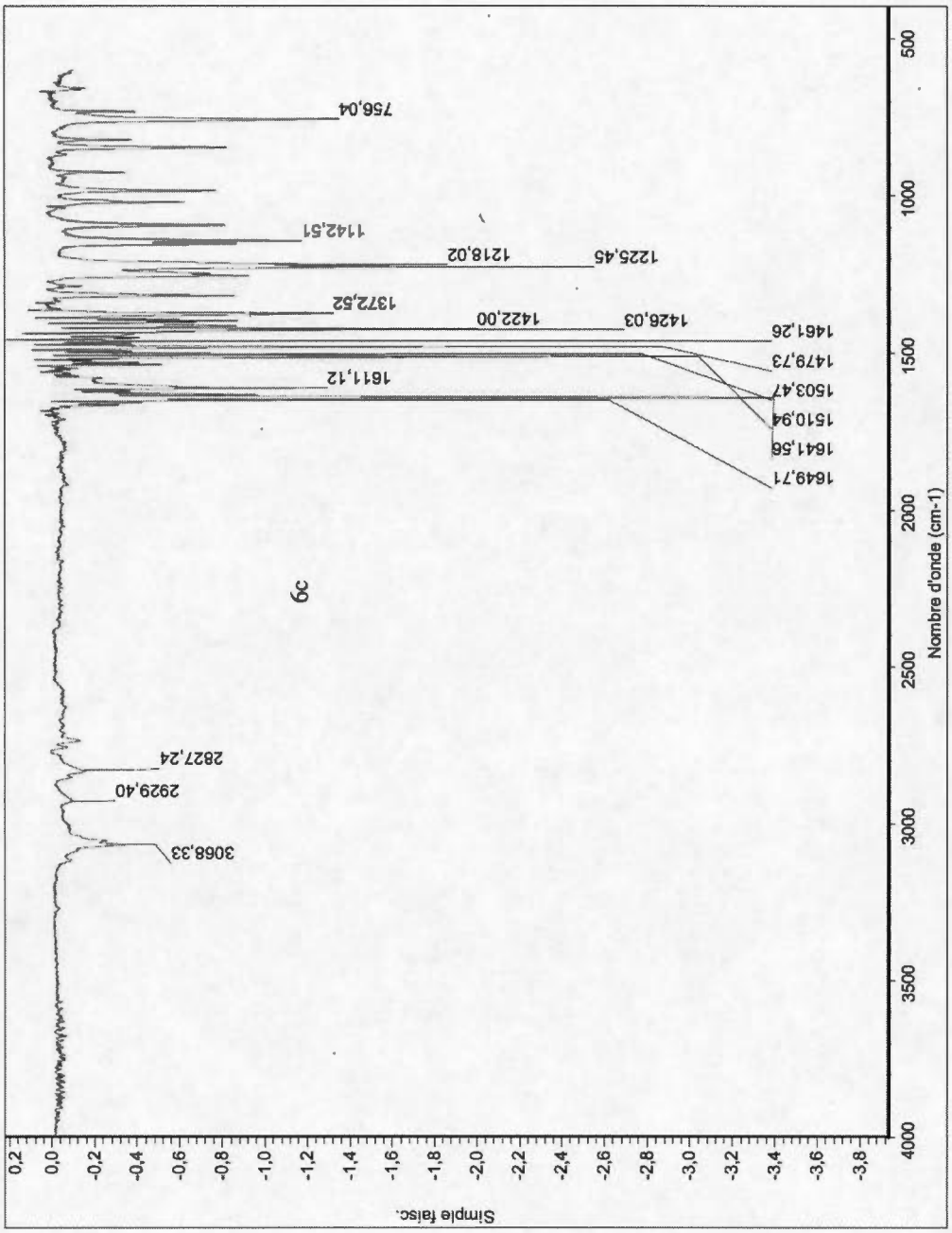

15.8486
61.4479
100.7462
111.1296
119.7500
122.3826
123.1249
123.4821
124.4078
124.4401
125.4188
126.8443
129.8316
137.4898
138.3301
141.7932
184.9606
6a
f1 (ppm)

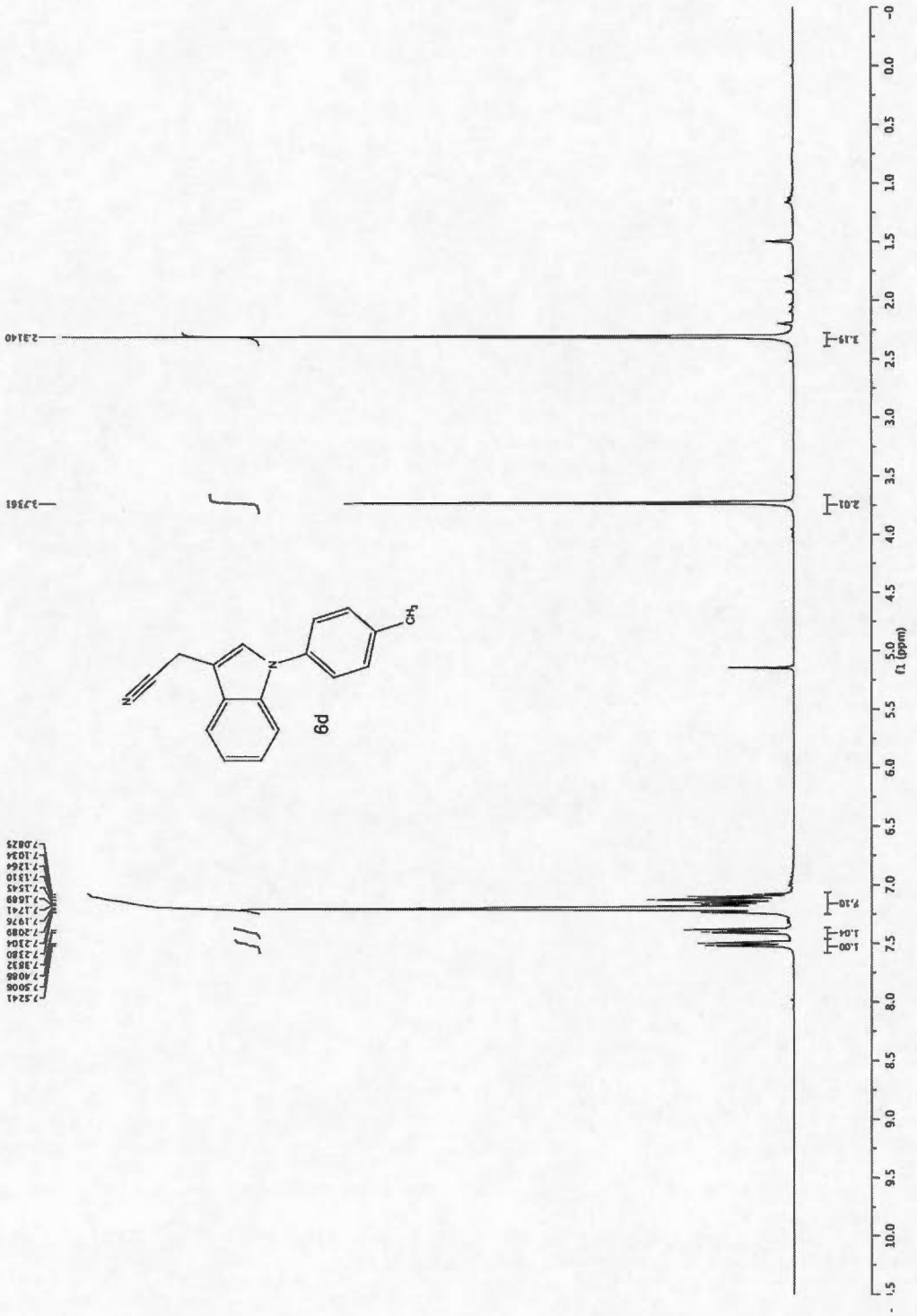

6a
Simple faisc.
Nombre d'onde (cm-1)
1665,48
1659,53
1536,18
1493,12
1479,63
1461,38
1453,47
1308,32
1224,08
1650,10
1605,02
1530,31
3117,37
3051,99
2966,17
2868,10
2806,81
2761,86
2725,09

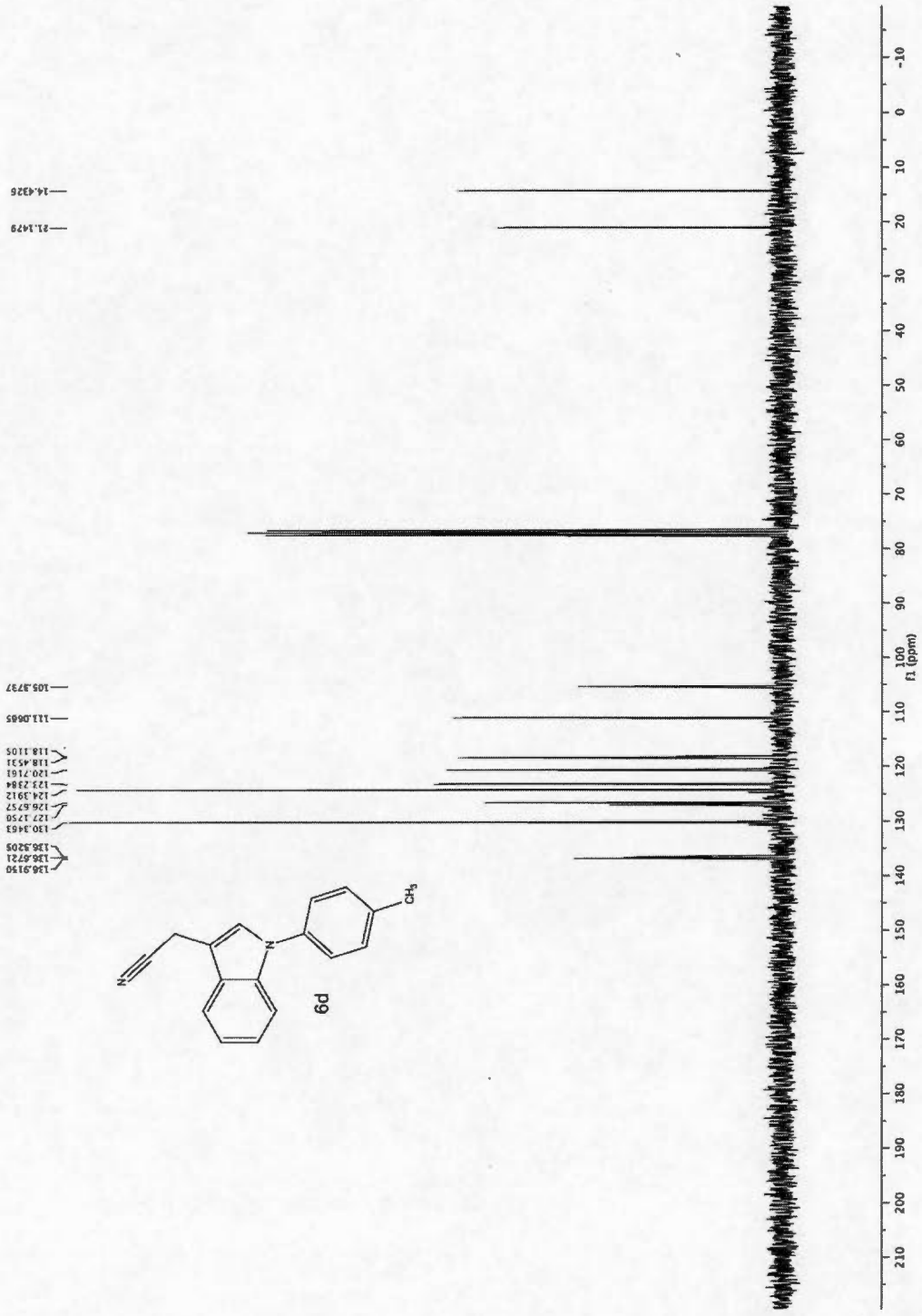

6b
f1 (ppm)

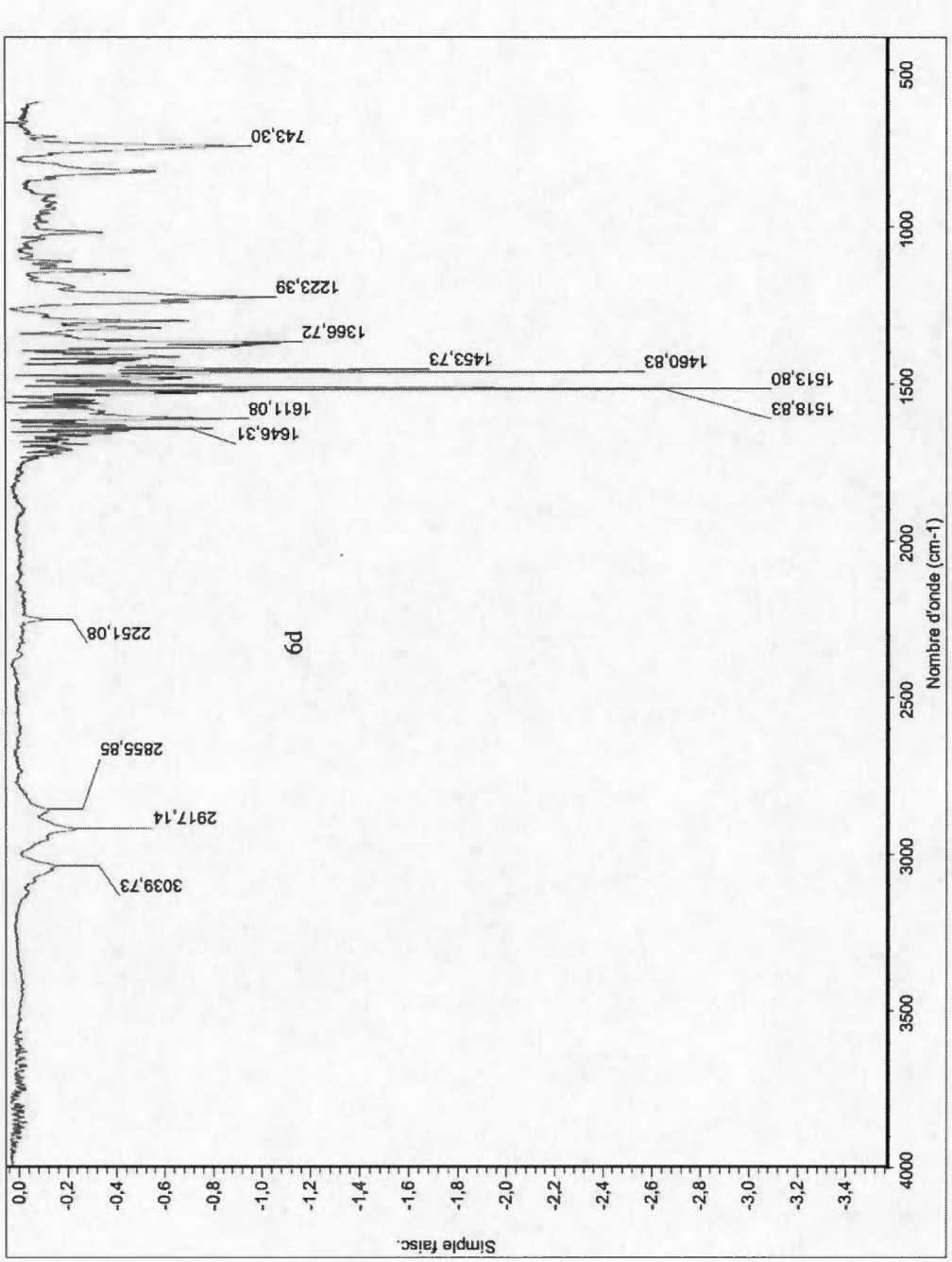

10.1456
8.3297
8.2038
7.7715
7.7593
7.7413
7.7362
7.7083
7.7018
7.6835
7.6831
7.6831
7.1712
7.1371
7.0927
6.8176
6.8906
2.4429
3.11
1.04
3.00
2.20
1.05
0.99
1.00
f1 (ppm)
8c

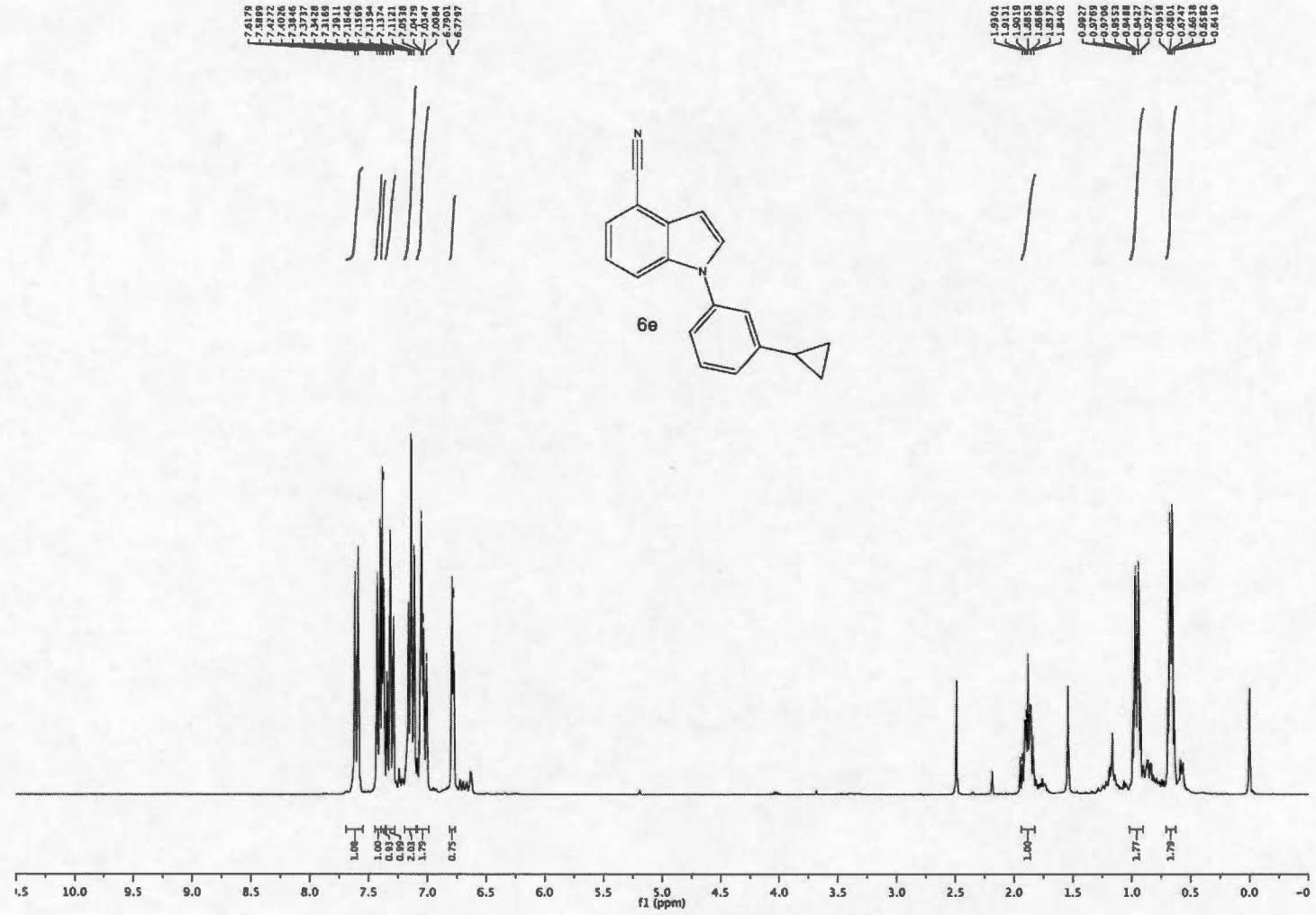

11.3896
110.4100
115.2760
117.0291
117.3929
120.8874
123.3797
123.7107
135.6508
129.9106
130.0276
131.9821
138.9289
147.7509
161.1512
164.4638
184.8037
6c
f1 (ppm)

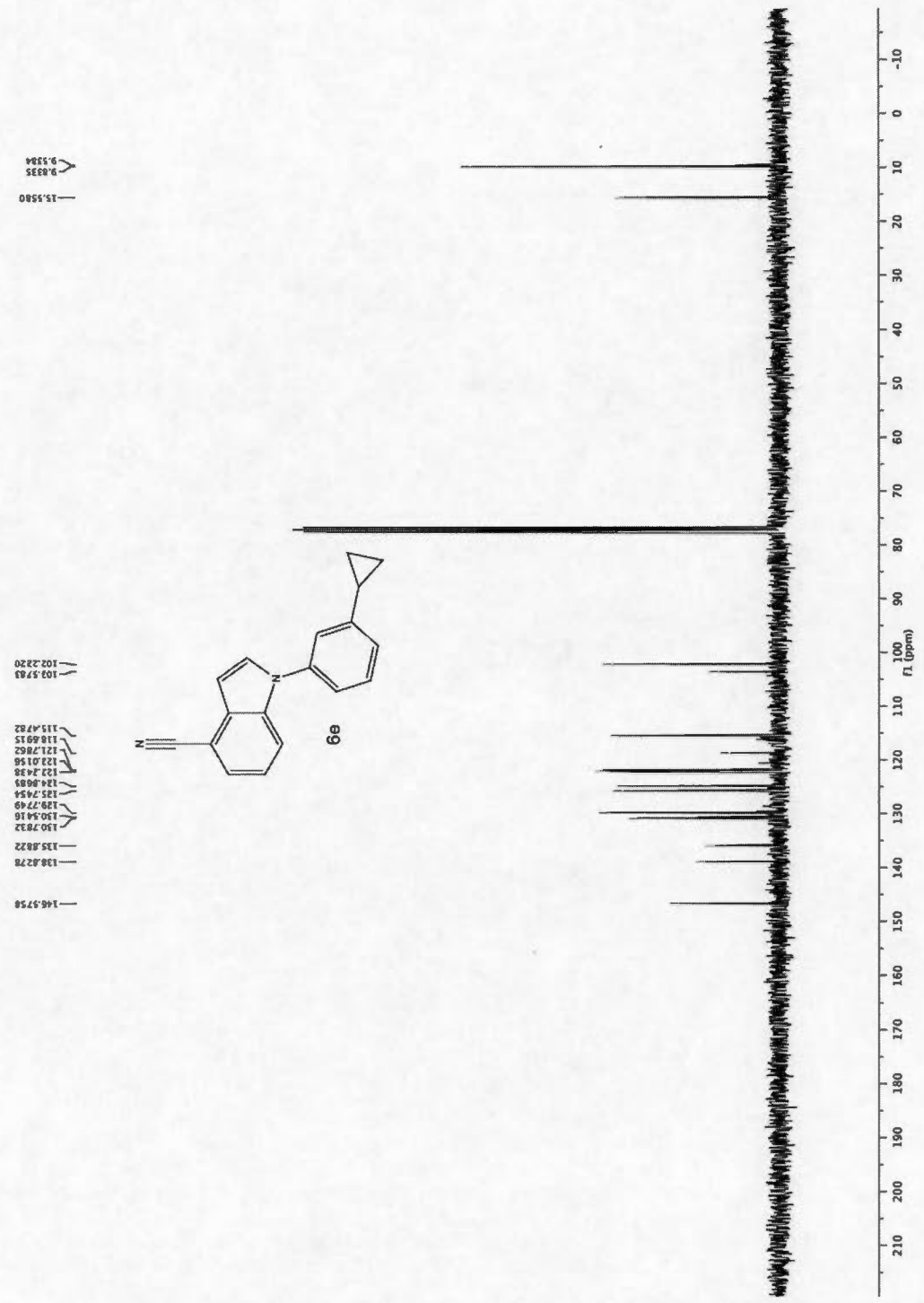

Simple talc.
0,2
0,0
-0,2
-0,4
-0,6
-0,8
-1,0
-1,2
-1,4
-1,6
-1,8
-2,0
-2,2
-2,4
-2,6
-2,8
-3,0
-3,2
-3,4
-3,6
-3,8
4000
3500
3000
2500
2000
1500
1000
500
Nombre d'onde (cm-1)
3068,33
2929,40
2827,24
1649,71
1641,56
1510,94
1503,47
1479,73
1461,26
1426,03
1422,00
1372,52
1225,45
1218,02
1142,51
756,04
3c

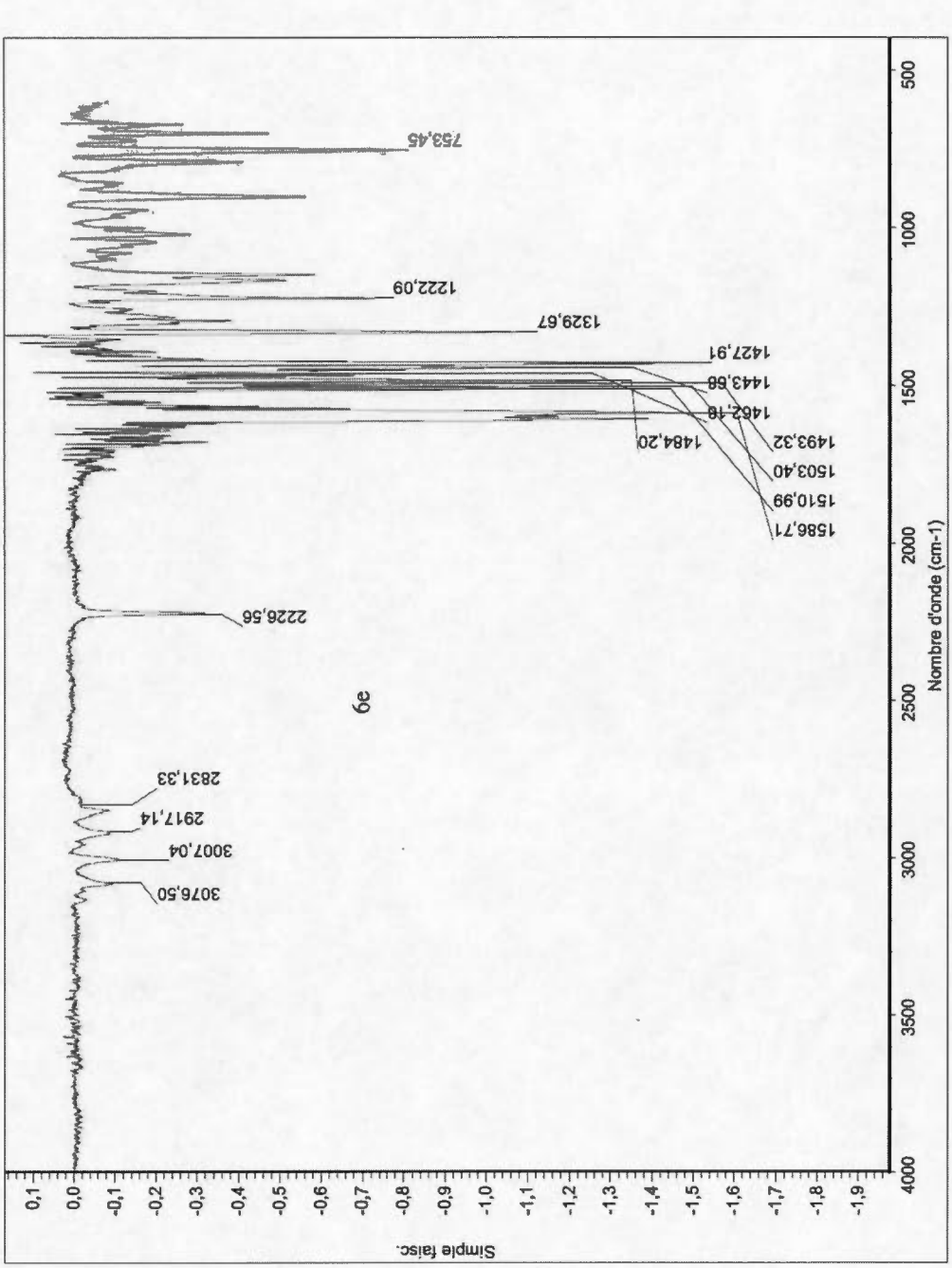

2.3140
3.7361
3.19
2.01
7.10
1.00
1.04
f1 (ppm)
9d

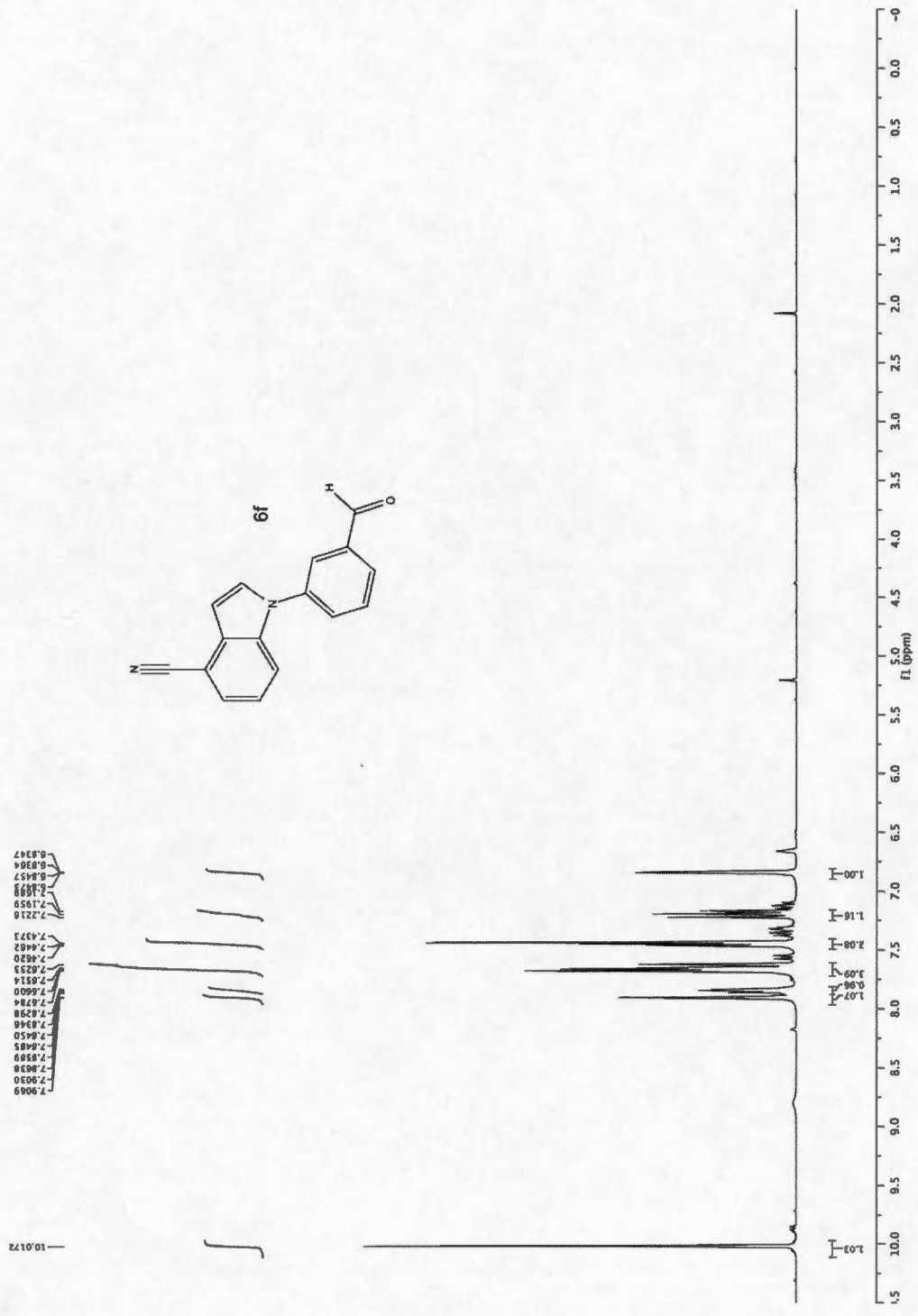

136.9190
136.8721
136.5205
130.3463
127.1750
126.8757
124.3912
123.2384
120.7161
118.4531
118.1105
111.0665
105.8737
21.1479
14.4326
f1 (ppm)
6d


Simple faisc.
0,0
-0,2
-0,4
-0,6
-0,8
-1,0
-1,2
-1,4
-1,6
-1,8
-2,0
-2,2
-2,4
-2,6
-2,8
-3,0
-3,2
-3,4
4000
3500
3000
2500
2000
1500
1000
500
Nombre d'onde (cm-1)
3039,73
2917,14
2855,85
2251,08
1646,31
1611,08
1518,83
1513,80
1460,83
1453,73
1366,72
1223,39
743,30
p9

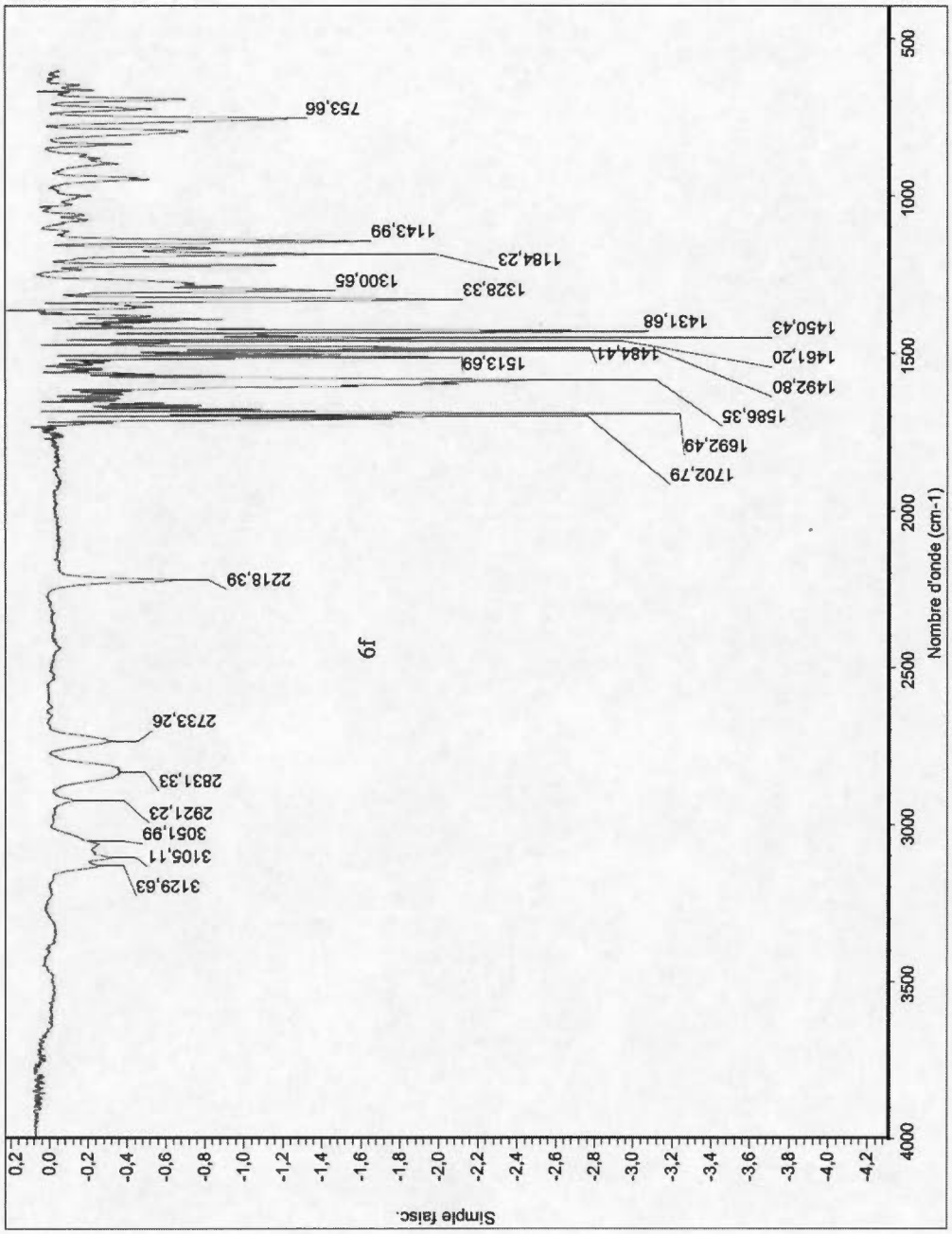

7.6179
7.5899
7.4172
7.4026
7.3846
7.3737
7.3428
7.3169
7.2911
7.1846
7.1569
7.1394
7.1334
7.1121
7.0538
7.0479
7.0347
7.0084
6.7901
6.7797
1.9301
1.9131
1.9019
1.8853
1.8696
1.8577
1.8402
0.9927
0.9769
0.9706
0.9553
0.9438
0.9277
0.6958
0.6801
0.6747
0.6638
0.6562
0.6419
N
N
6e
1.00
1.00
0.93
0.99
2.03
1.79
0.75
1.00
1.77
1.79
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

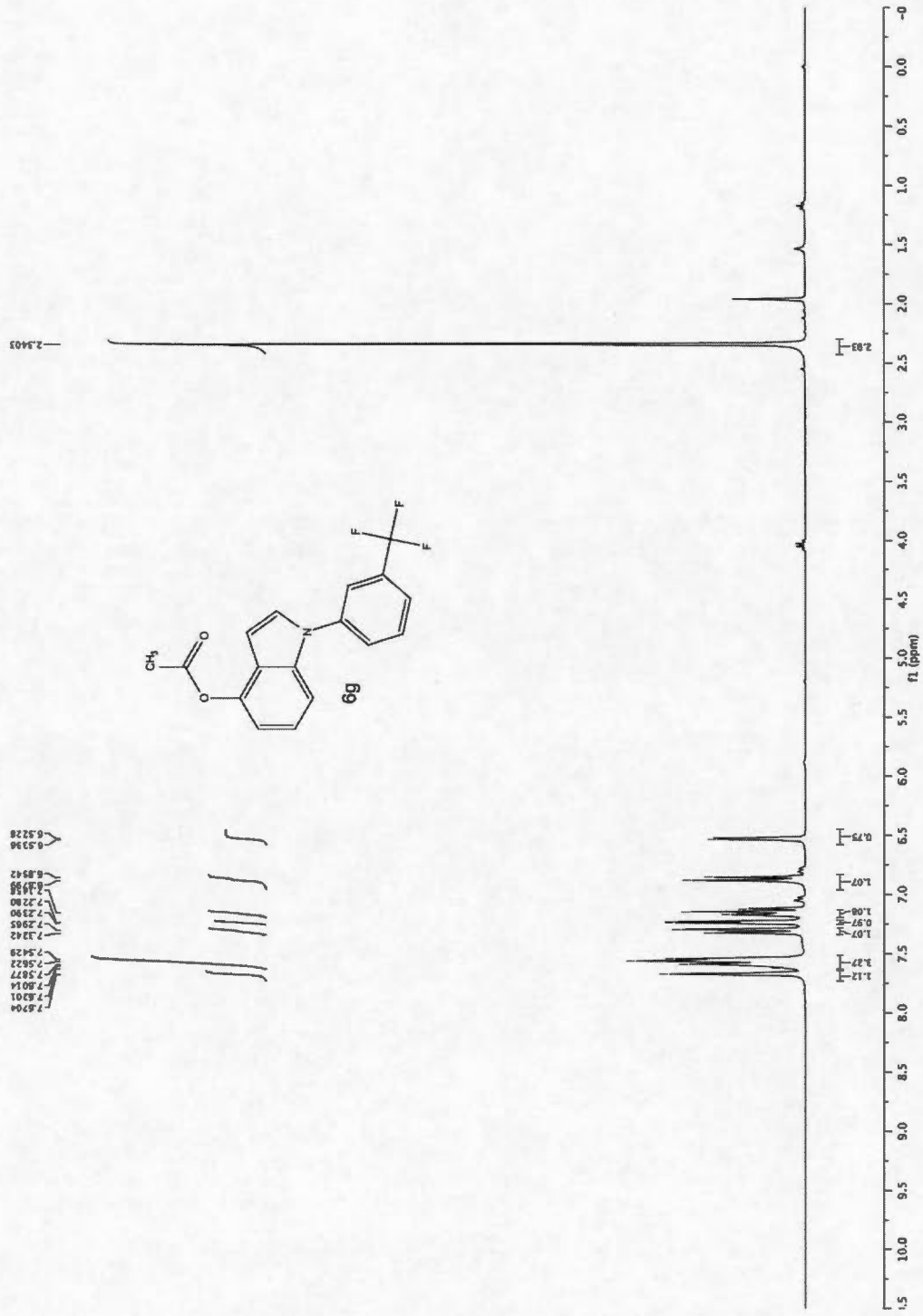

9.8335
9.5384
15.5580
102.2220
103.5783
115.4782
118.6915
121.7862
123.0156
123.2438
124.9085
125.7454
129.2749
130.5416
130.7832
135.8022
138.8278
146.5758
6e
N
N
f1 (ppm)

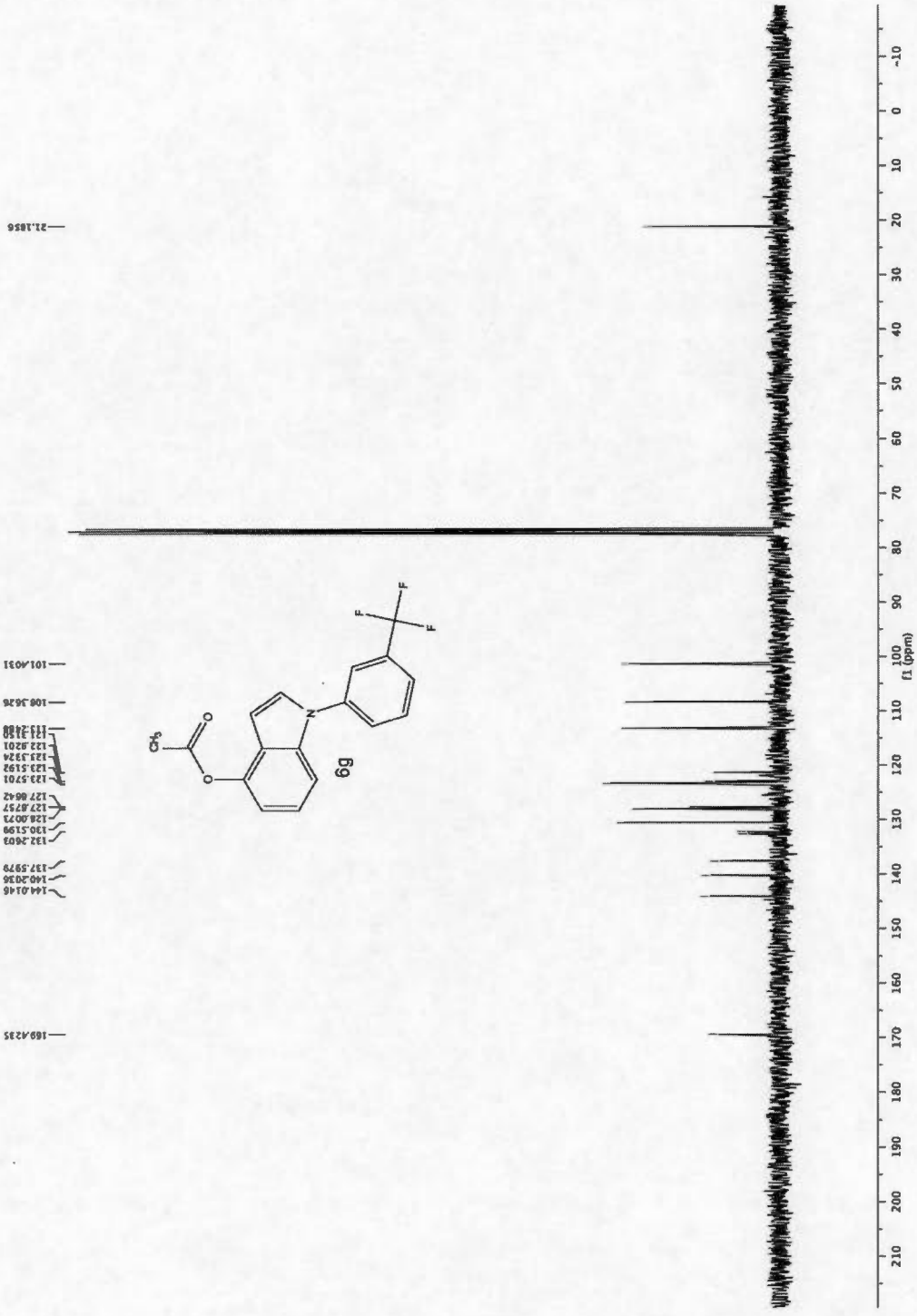

Simple faisc.
0,1
0,0
-0,1
-0,2
-0,3
-0,4
-0,5
-0,6
-0,7
-0,8
-0,9
-1,0
-1,1
-1,2
-1,3
-1,4
-1,5
-1,6
-1,7
-1,8
-1,9
4000
3500
3000
2500
2000
1500
1000
500
Nombre d'onde (cm-1)
3076,50
3007,04
2917,14
2831,33
2226,56
1586,71
1510,99
1503,40
1493,32
1484,20
1462,18
1443,68
1427,91
1329,67
1222,09
753,45
9e

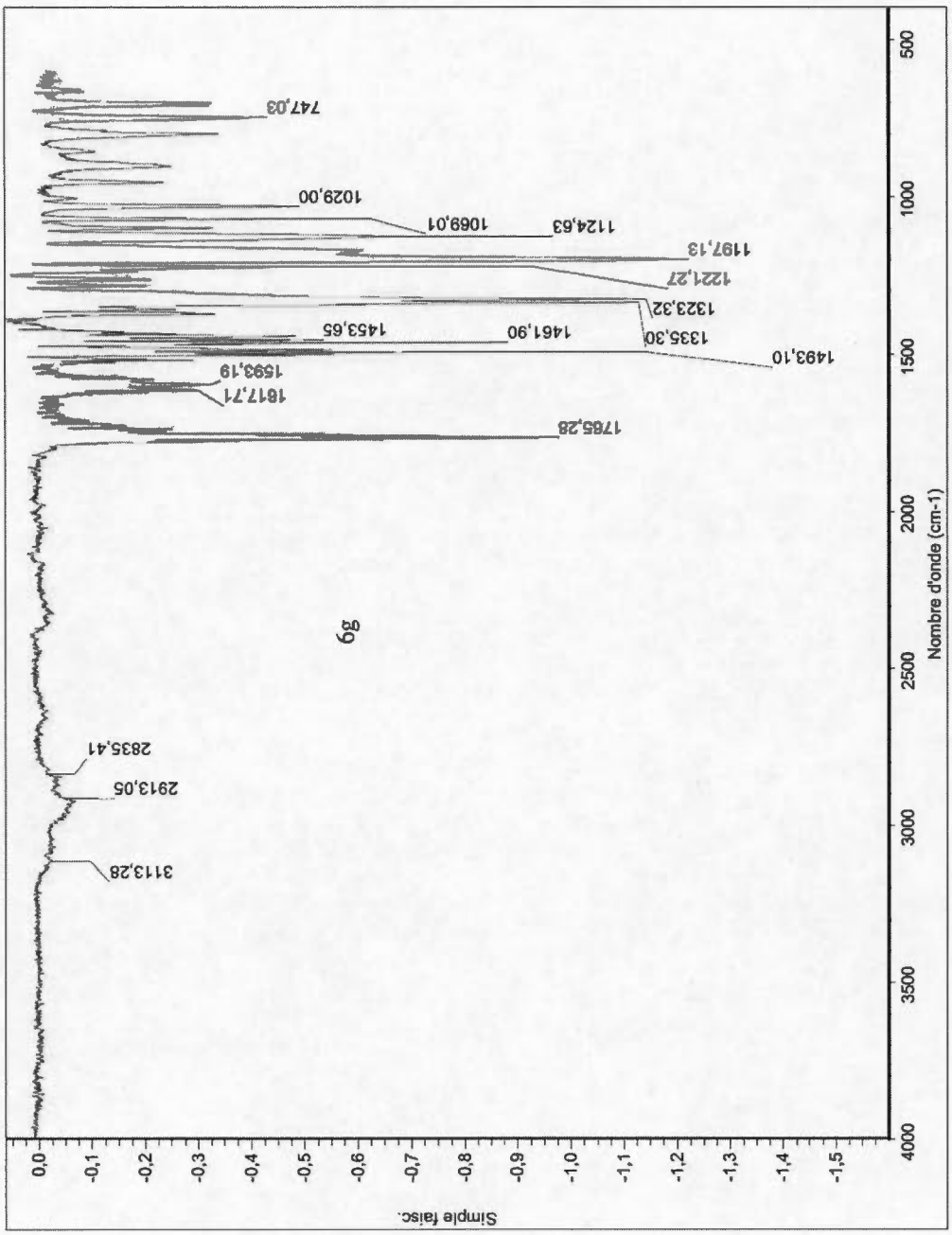

6f
H
O
N
N
10.0172
7.9069
7.9030
7.8838
7.8589
7.8485
7.8450
7.8348
7.8298
7.8244
7.8144
7.8114
7.8060
7.8033
7.4620
7.4462
7.4373
7.2216
7.1959
7.1899
6.8457
6.8364
6.8347
1.00
1.16
2.08
3.09
0.96
1.07
1.03
f1 (ppm)

6f
f1 (ppm)

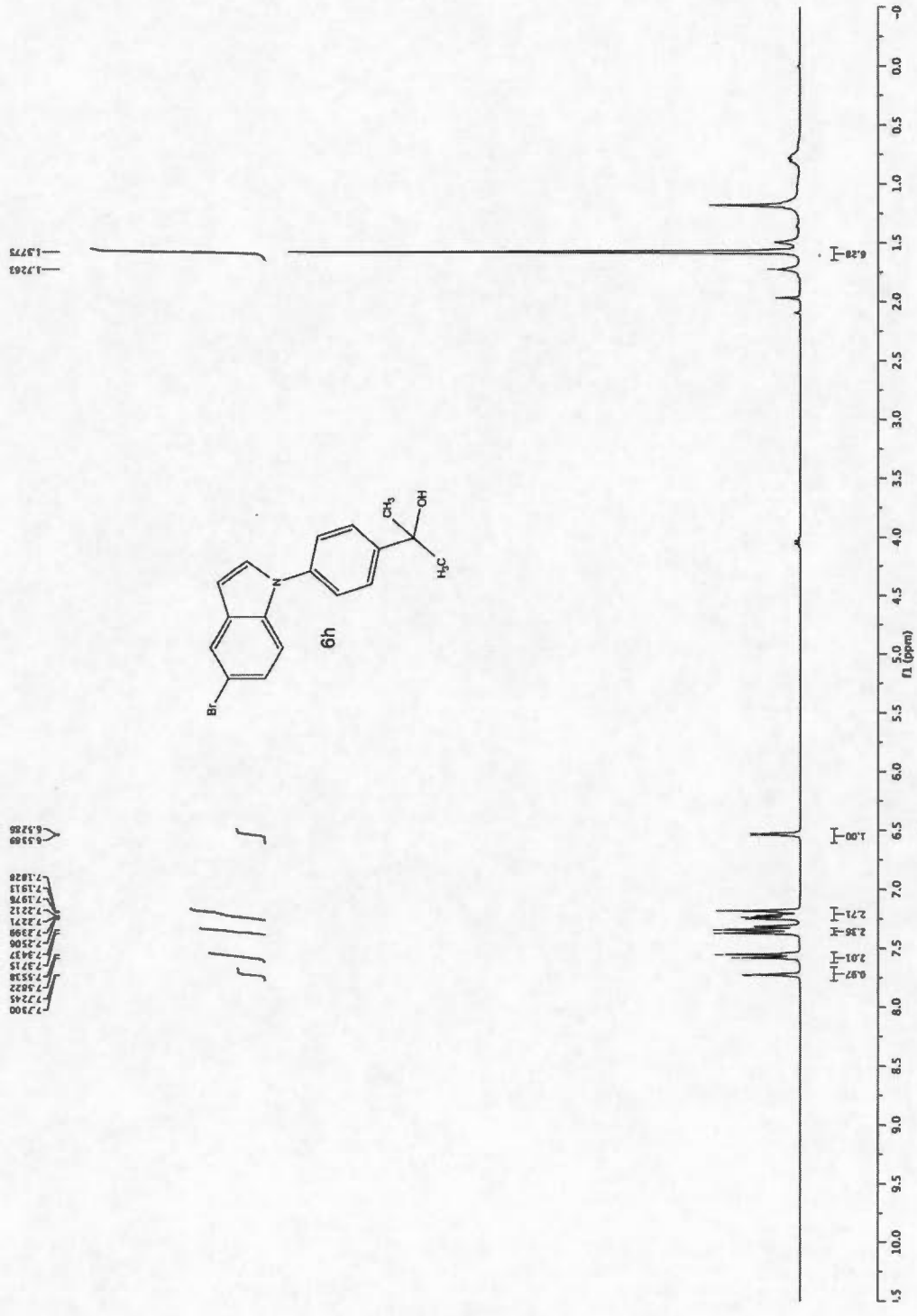

Simple faisc.
Nombre d'onde (cm-1)
753,66
1143,99
1184,23
1328,33
1300,65
1431,68
1450,43
1461,20
1484,41
1513,69
1492,80
1586,35
1692,49
1702,79
2218,39
2733,26
2831,33
2921,23
3051,99
3105,11
3129,63
6f

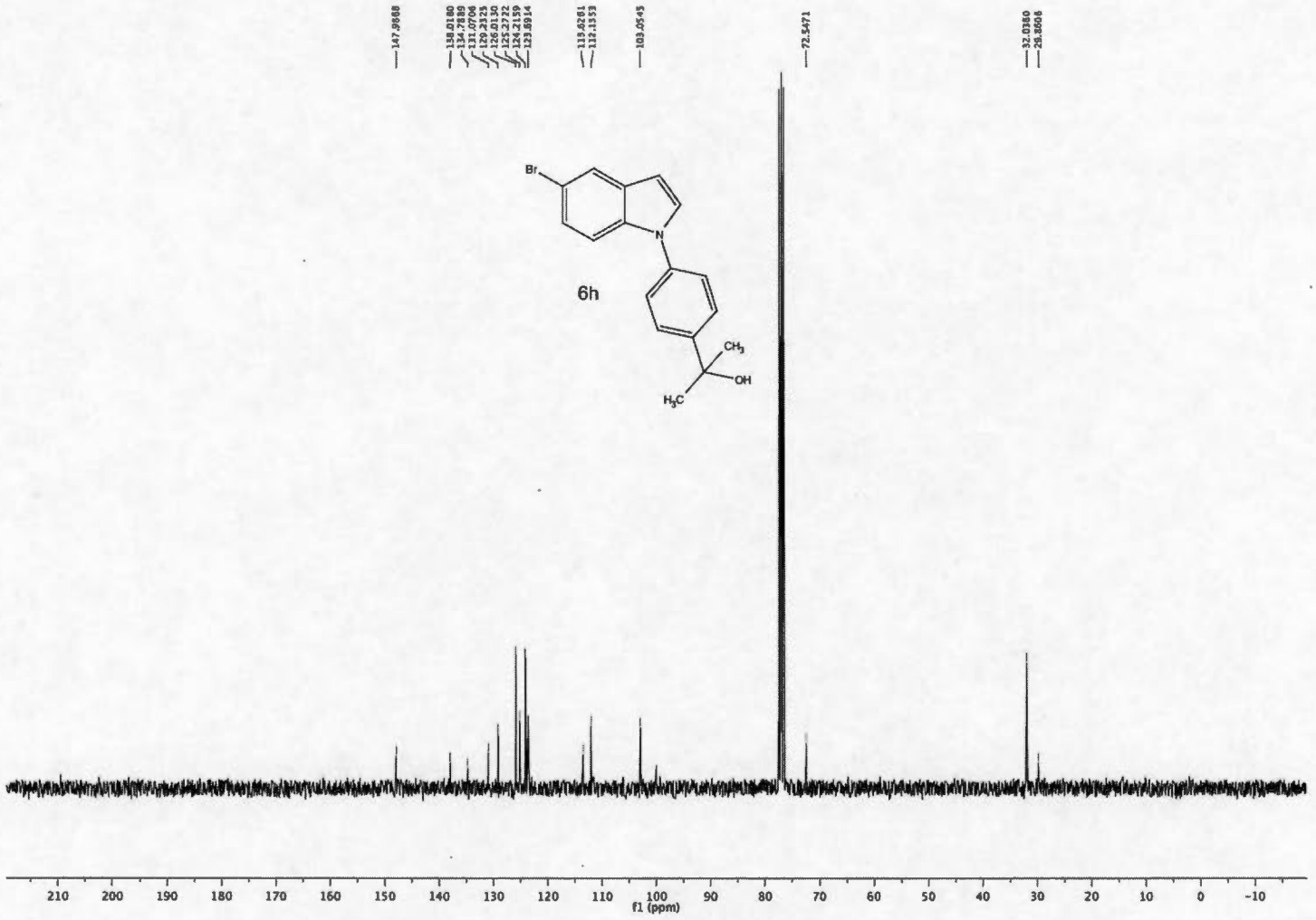

6g
f1 (ppm)

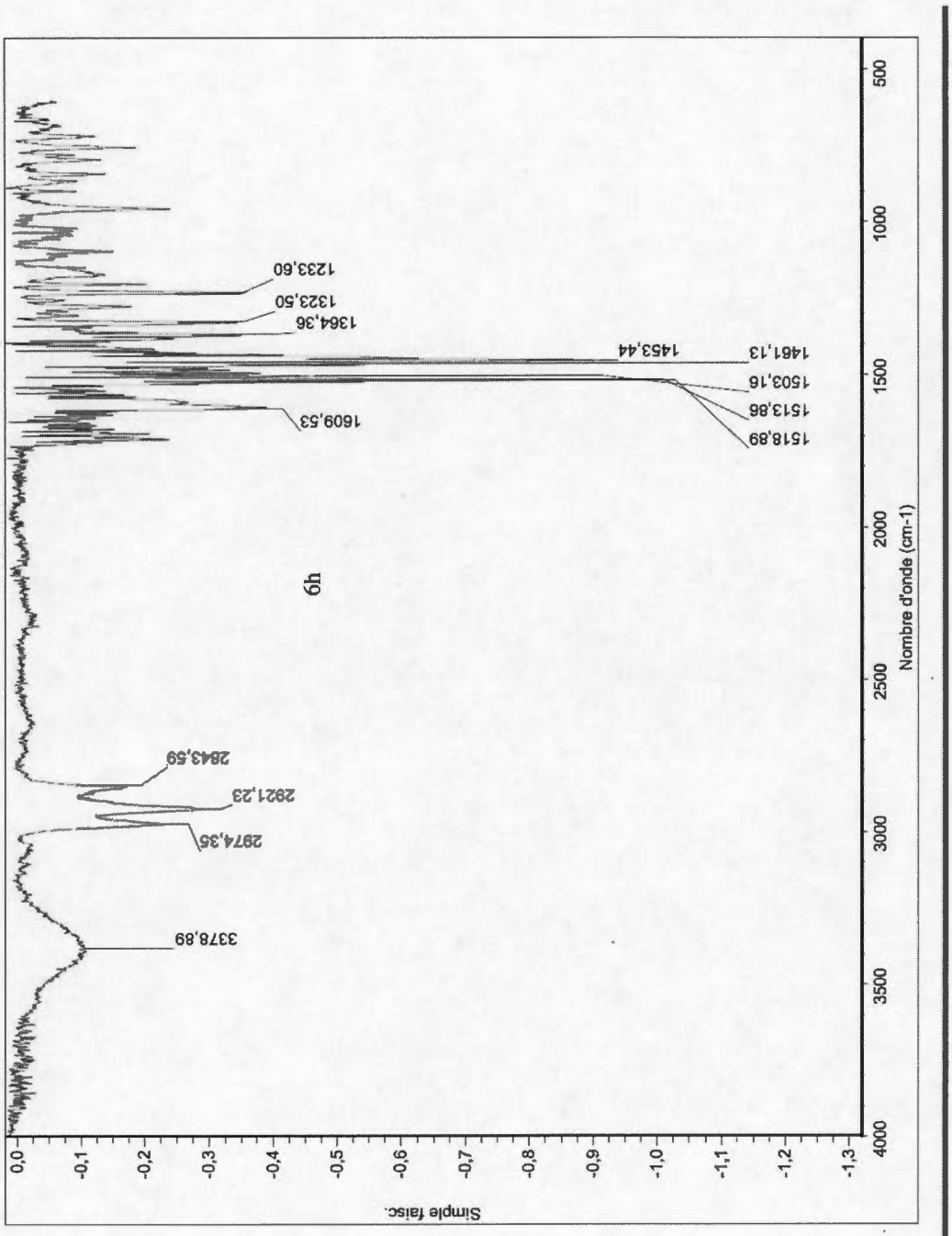

21.1856
101.4031
106.3626
123.5701
123.5192
123.3324
123.2201
127.8757
128.0073
130.5199
132.2603
137.5979
144.0146
169.4235
6g
F
F
F
O
O
N
CH3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

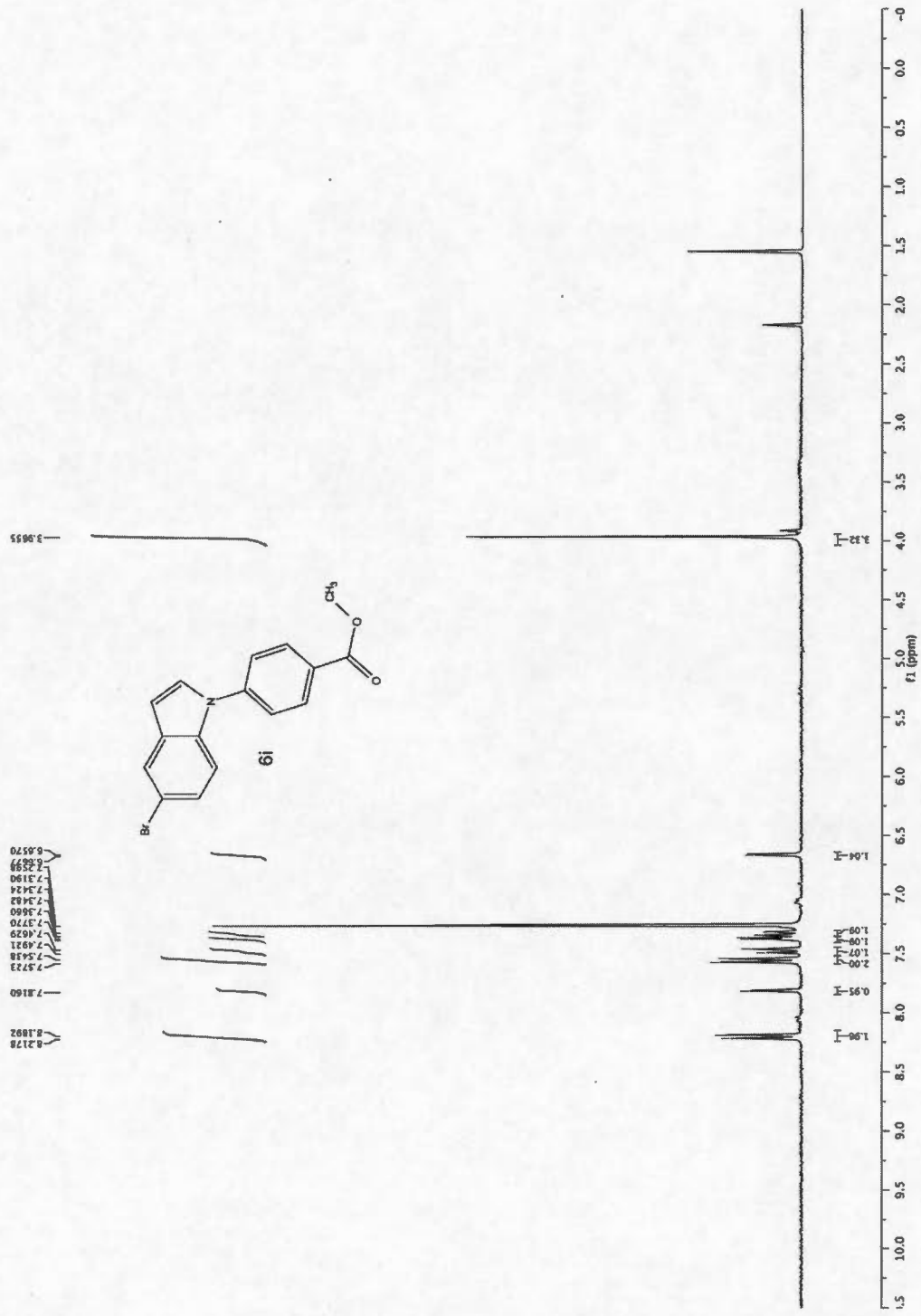

Simple talc.
0,0
-0,1
-0,2
-0,3
-0,4
-0,5
-0,6
-0,7
-0,8
-0,9
-1,0
-1,1
-1,2
-1,3
-1,4
-1,5
4000
3500
3000
2500
2000
1500
1000
500
Nombre d'onde (cm-1)
3113,28
2913,05
2835,41
1785,28
1617,71
1593,19
1493,10
1461,90
1453,65
1335,30
1323,32
1221,27
1197,13
1124,63
1069,01
1029,00
747,03

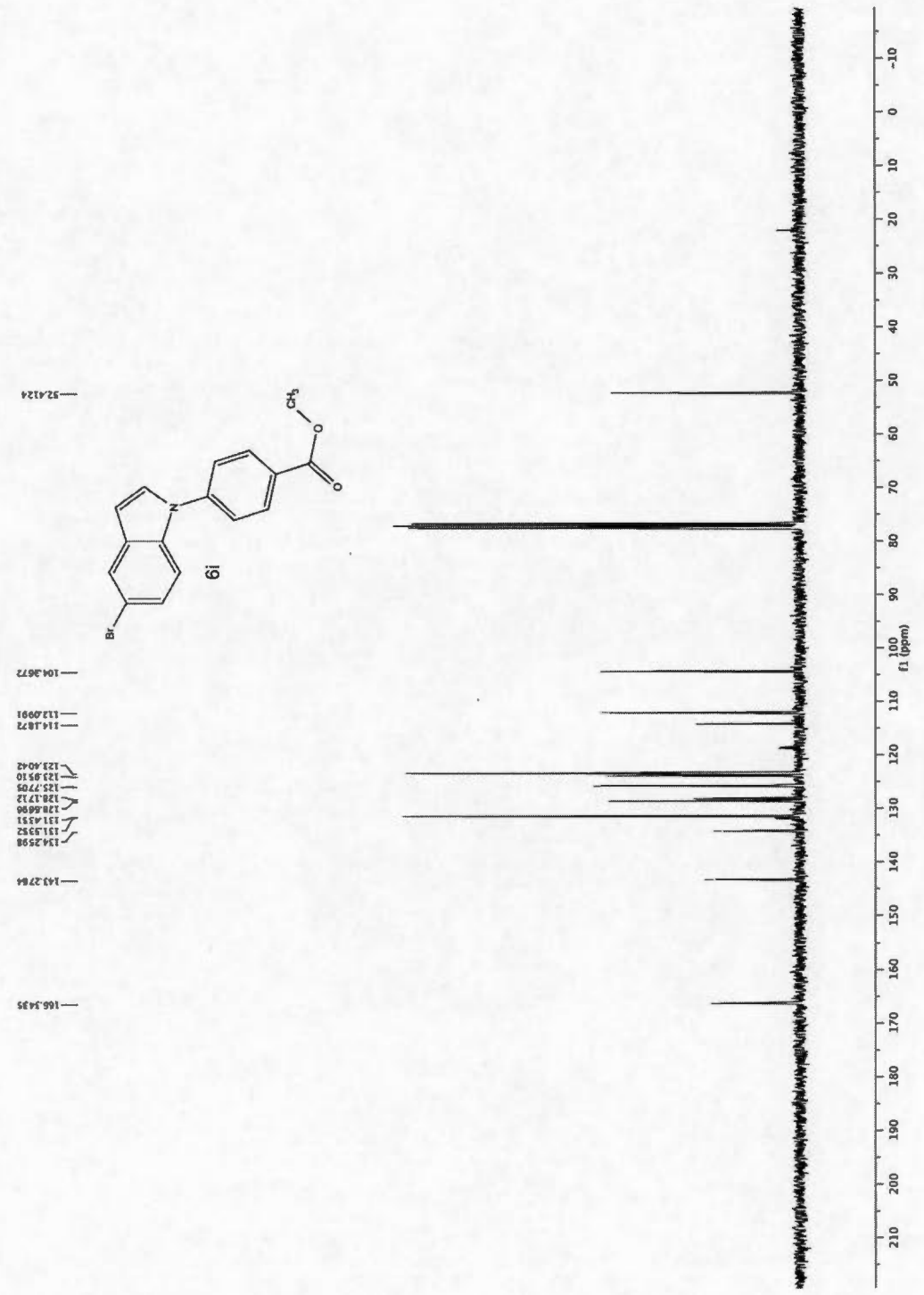
Fig

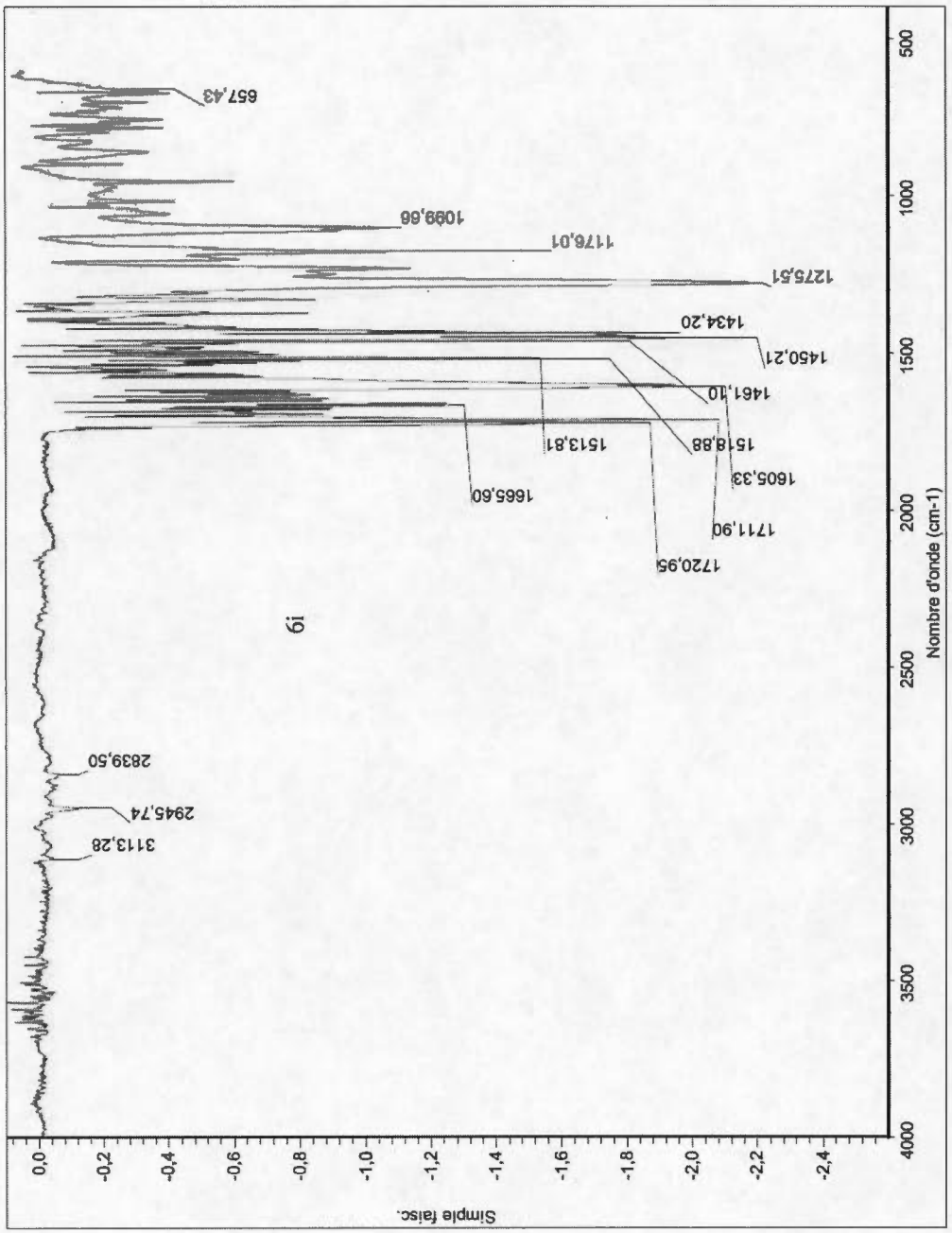

6h
Br
N
OH
CH3
H3C
f1 (ppm)

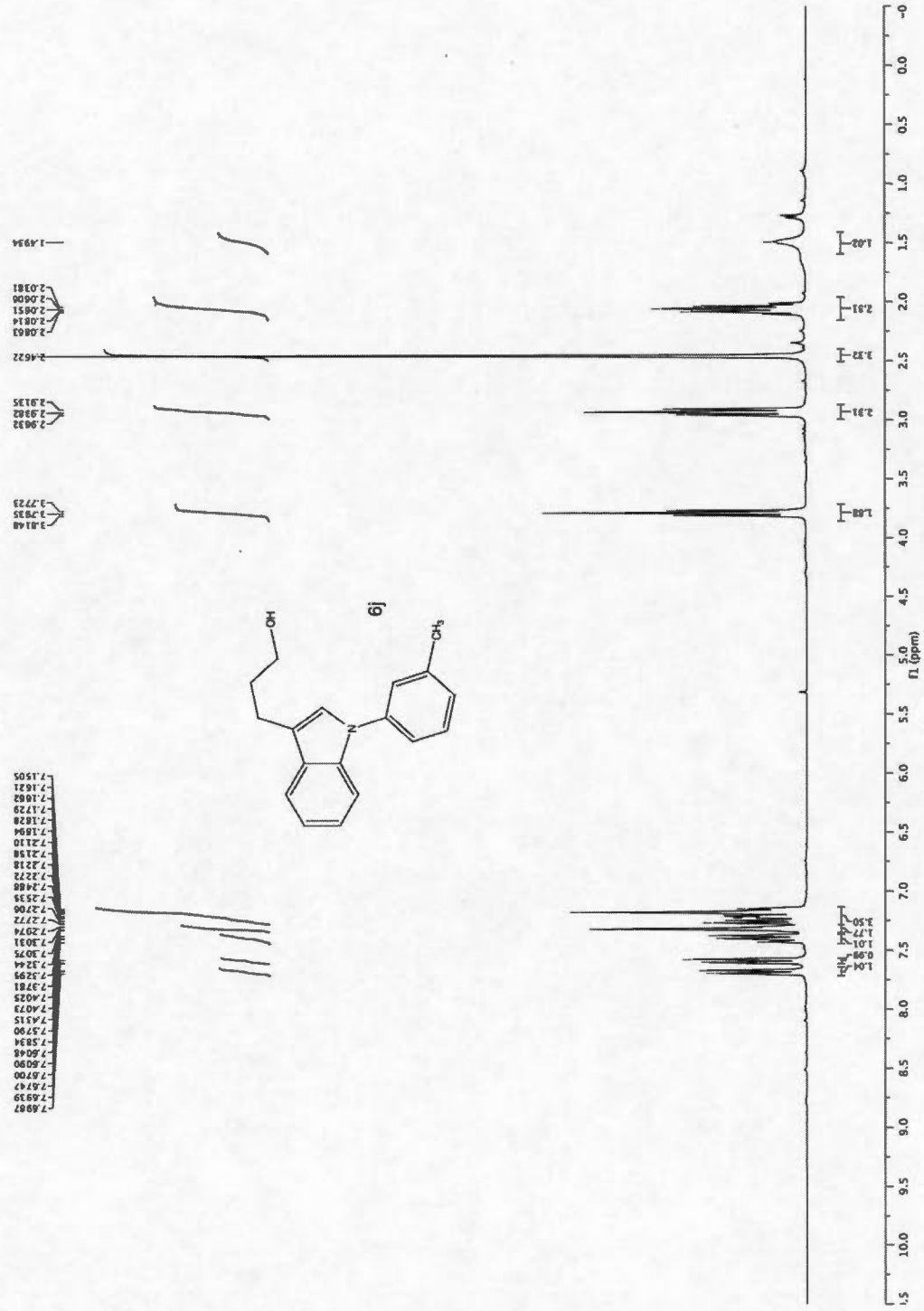

147.9888
138.0180
134.7188
131.0706
129.2323
126.0130
125.2722
124.2159
123.8914
119.4261
112.1353
103.0545
72.5471
32.0380
29.8506
Br
N
6h
CH3
OH
H3C
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


9g
3378,89
2974,35
2921,23
2843,59
1609,53
1518,89
1513,86
1503,16
1461,13
1453,44
1364,36
1323,50
1233,60
Simple faisc.
Nombre d'onde (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
0,0
-0,1
-0,2
-0,3
-0,4
-0,5
-0,6
-0,7
-0,8
-0,9
-1,0
-1,1
-1,2
-1,3

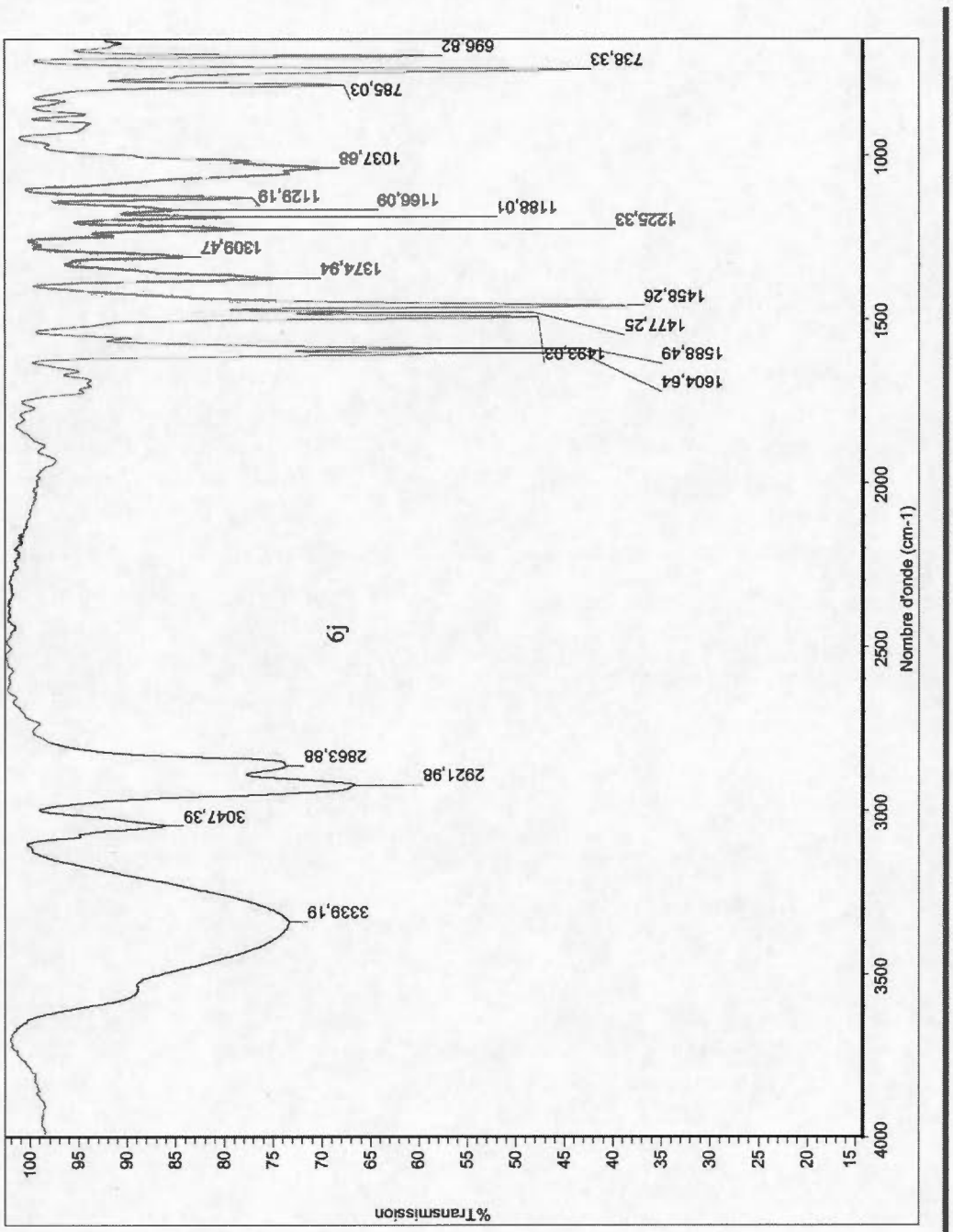

6i
Br
O
O
CH3
N
f1 (ppm)


52.4124
104.3672
112.0991
114.1872
123.4042
123.9510
125.7705
128.1712
128.6690
131.4251
131.5952
134.2598
143.2764
166.3435
6i
Br
CH3
O
O
N
f1 (ppm)

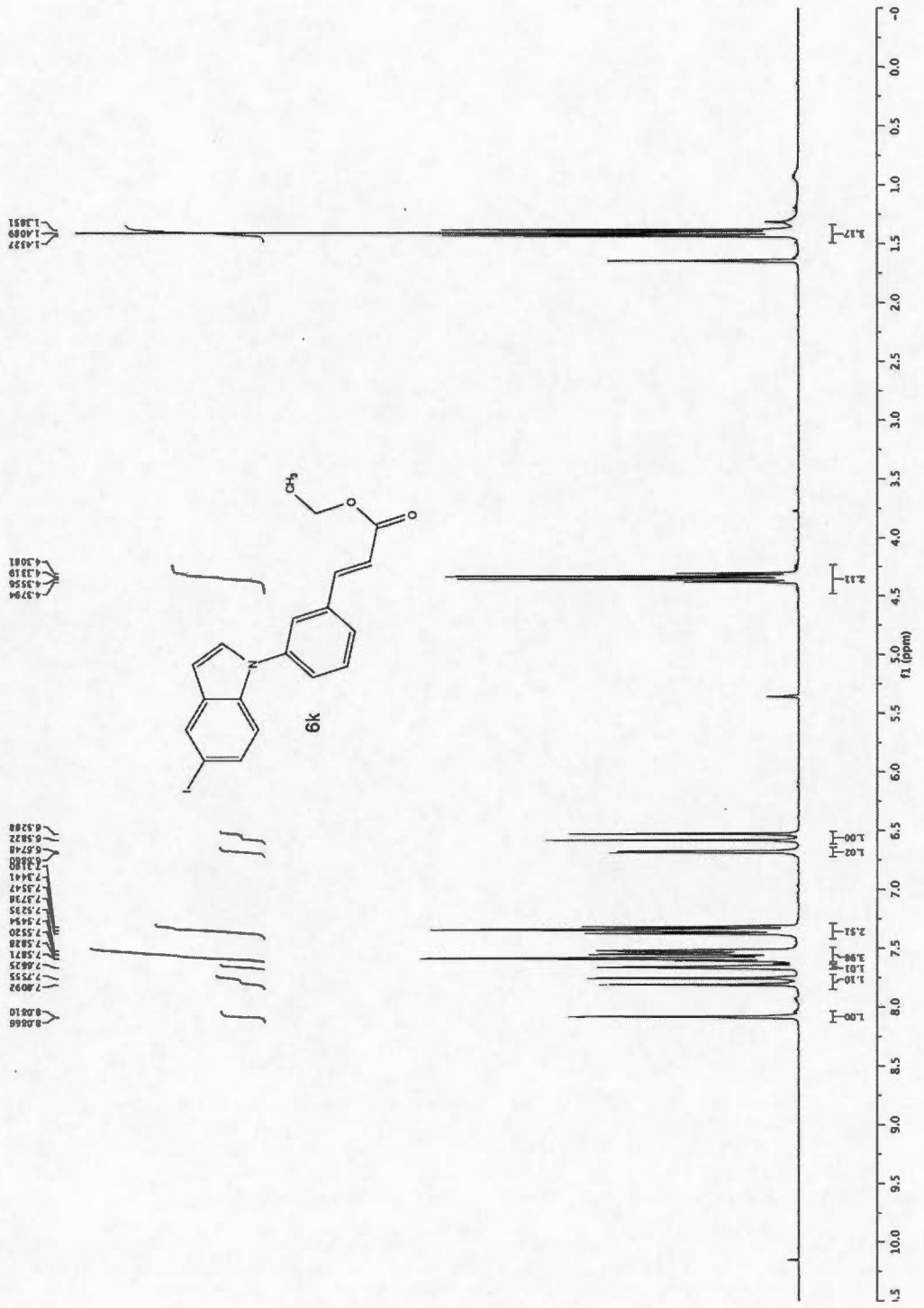

Simple faisc.
0,0
-0,2
-0,4
-0,6
-0,8
-1,0
-1,2
-1,4
-1,6
-1,8
-2,0
-2,2
-2,4
4000
3500
3000
2500
2000
1500
1000
500
Nombre d'onde (cm-1)
3113,28
2945,74
2839,50
1720,95
1711,90
1665,60
1605,33
1518,88
1513,81
1461,10
1450,21
1434,20
1275,51
1176,01
1099,66
657,43

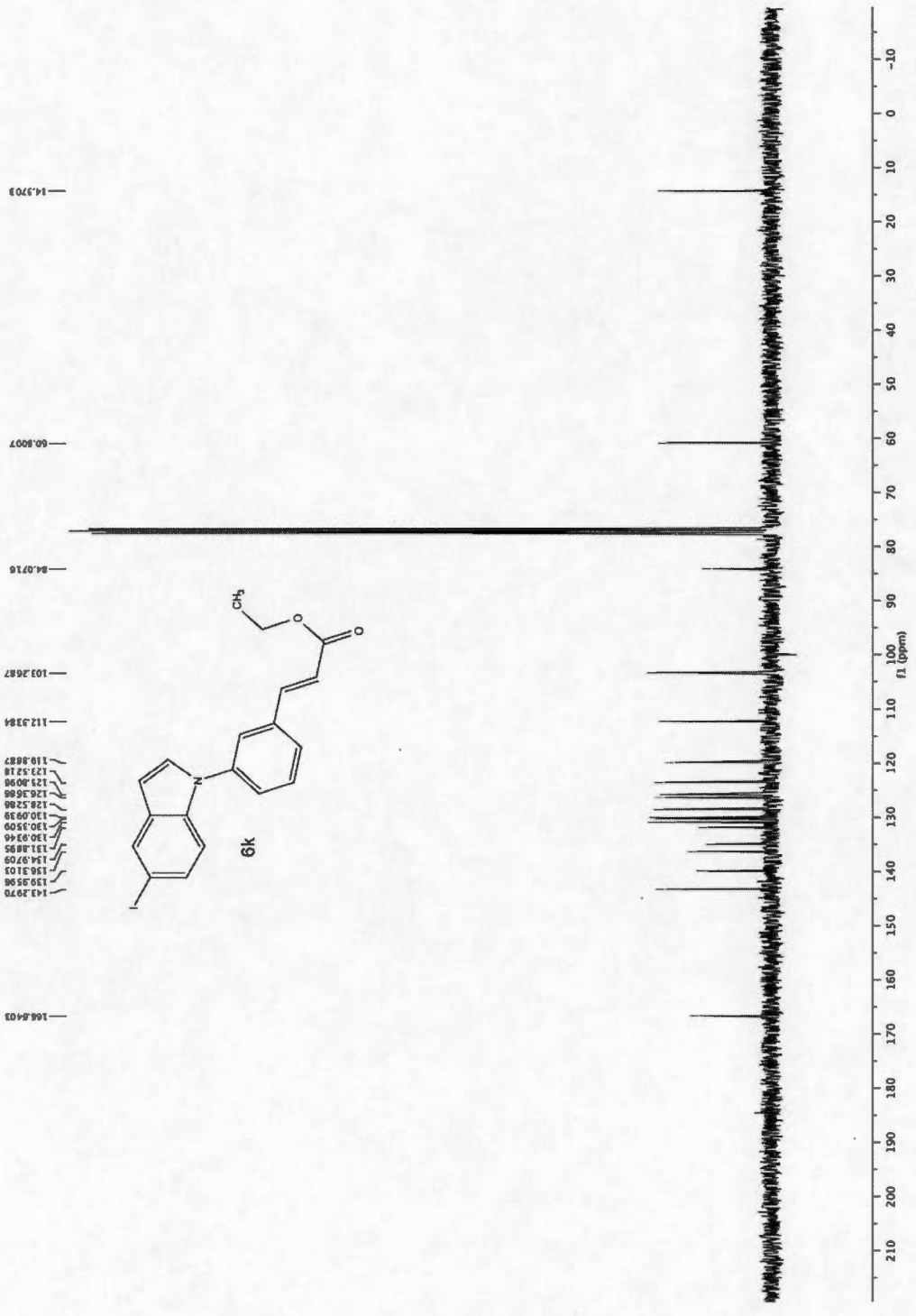

6j
OH
CH3
N
f1 (ppm)

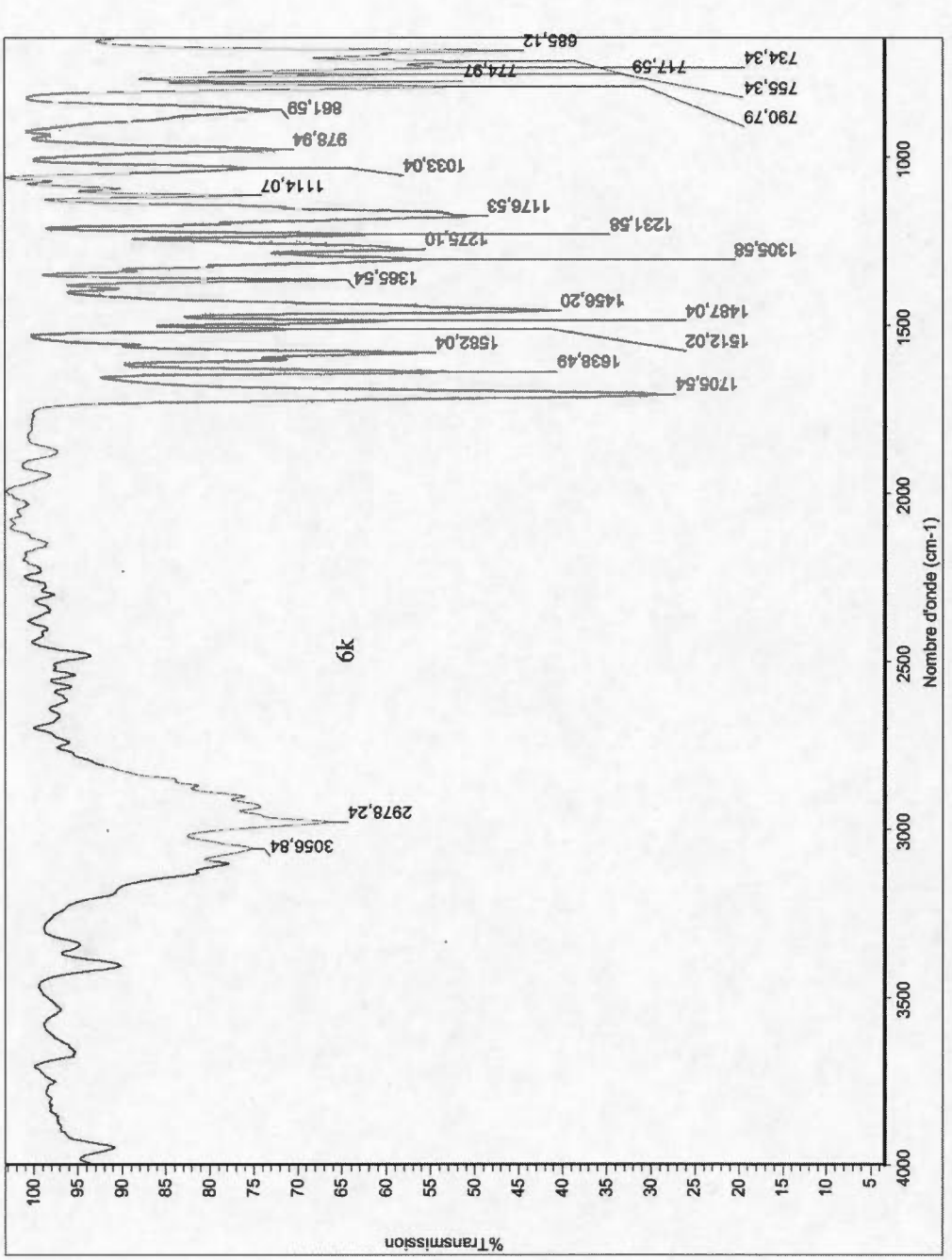
21.5448
21.3078
32.9291
62.6798
110.8695
116.9072
119.2531
119.3084
121.1510
122.4063
124.7521
125.2630
126.8956
128.8626
129.3953
130.1488
139.0554
139.8666
OH
N
CH3
6j
f1 (ppm)

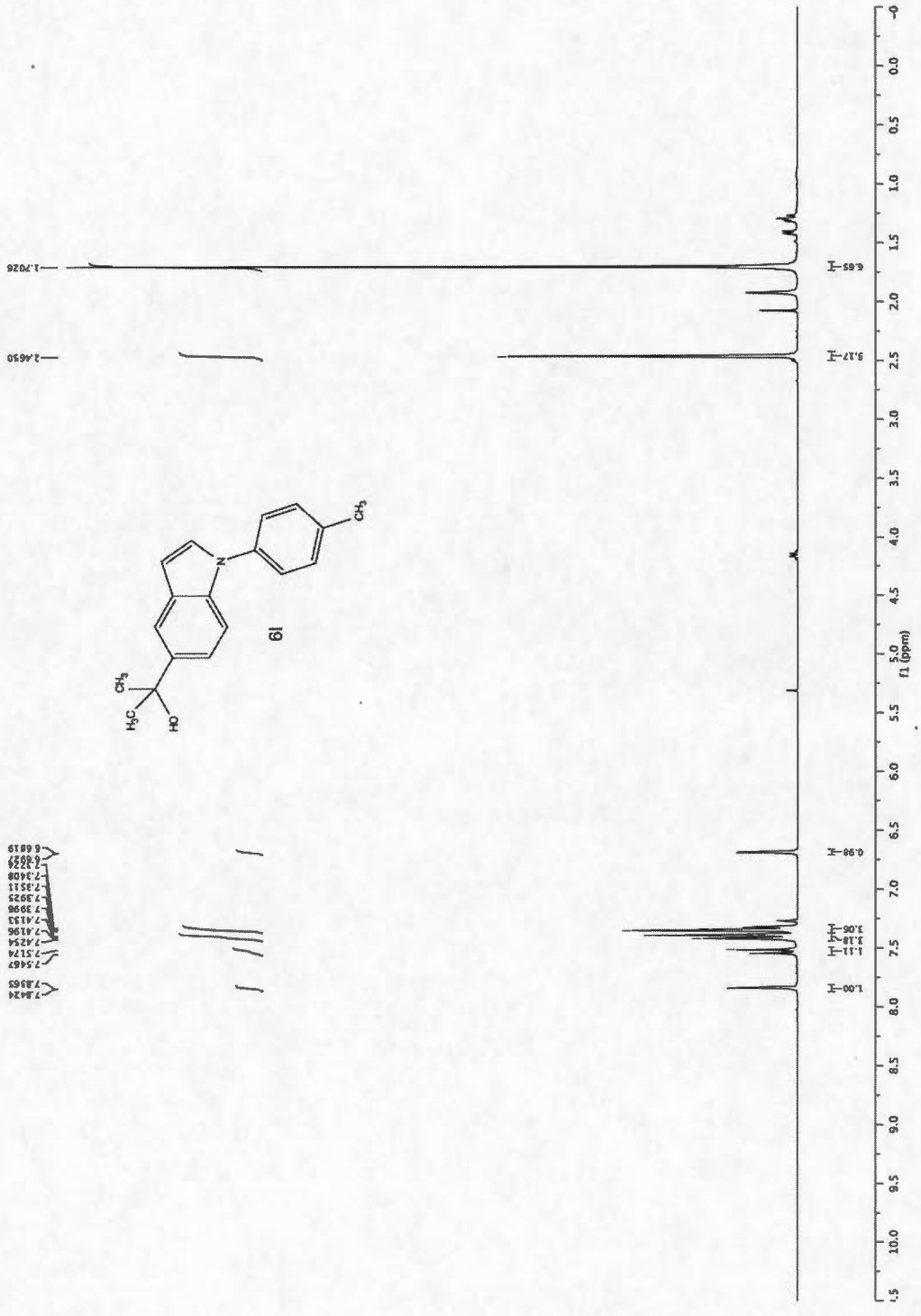

%Transmission
Nombre d'onde (cm-1)
3338,19
3047,39
2921,98
2863,88
1604,64
1588,49
1493,02
1477,25
1458,26
1374,94
1309,47
1225,33
1188,01
1166,09
1128,19
1037,88
785,03
738,33
696,82

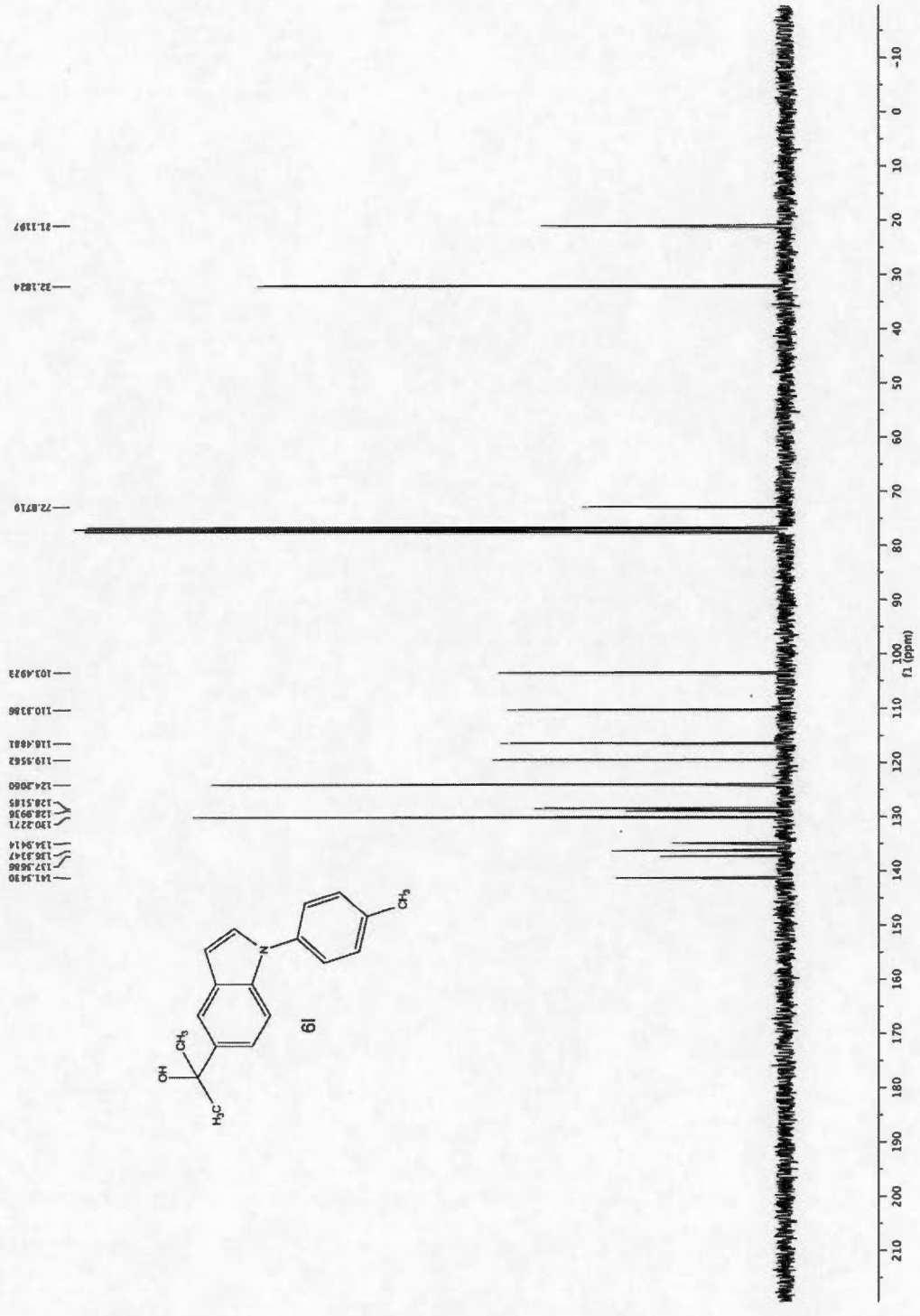
6j

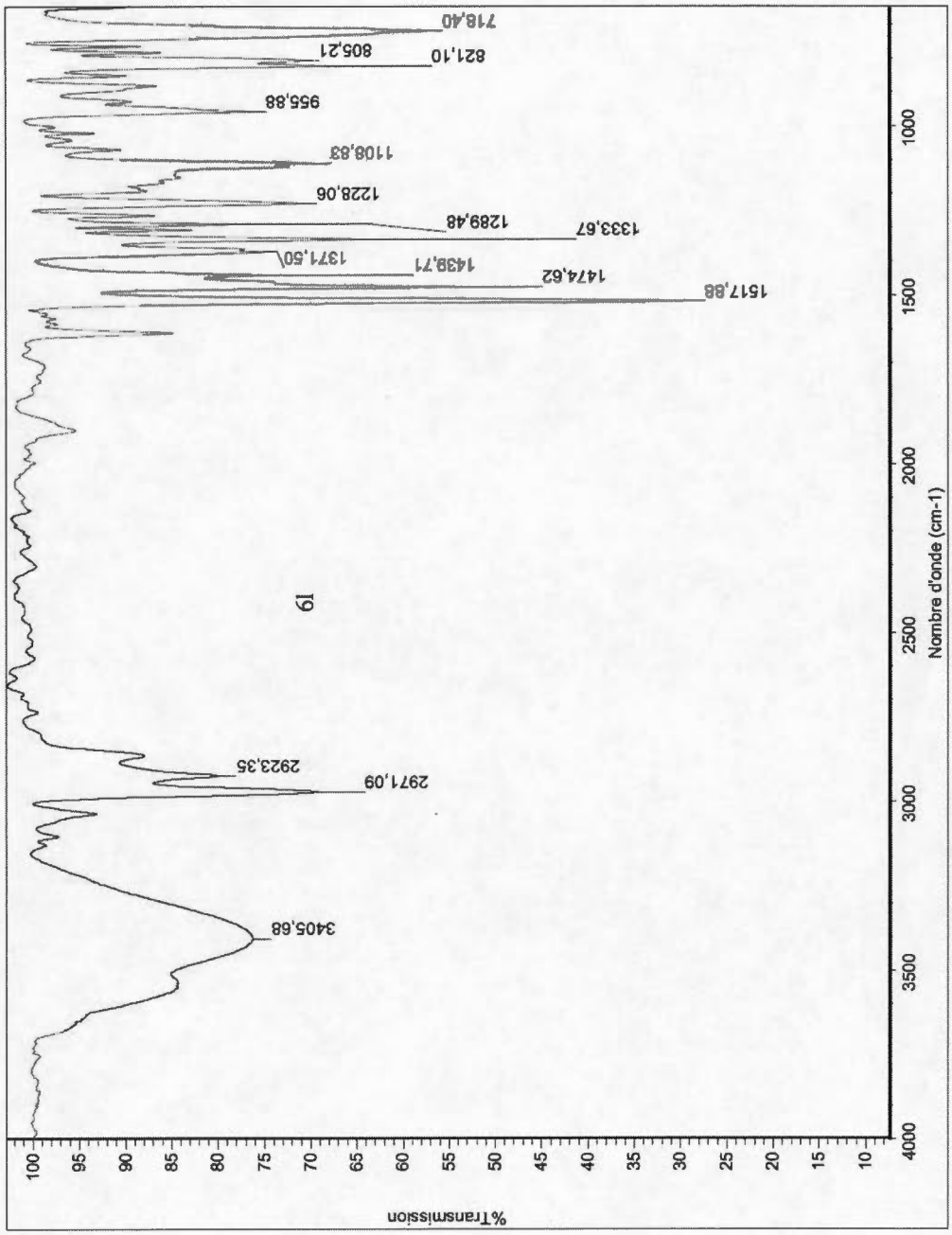

6k
f1 (ppm)

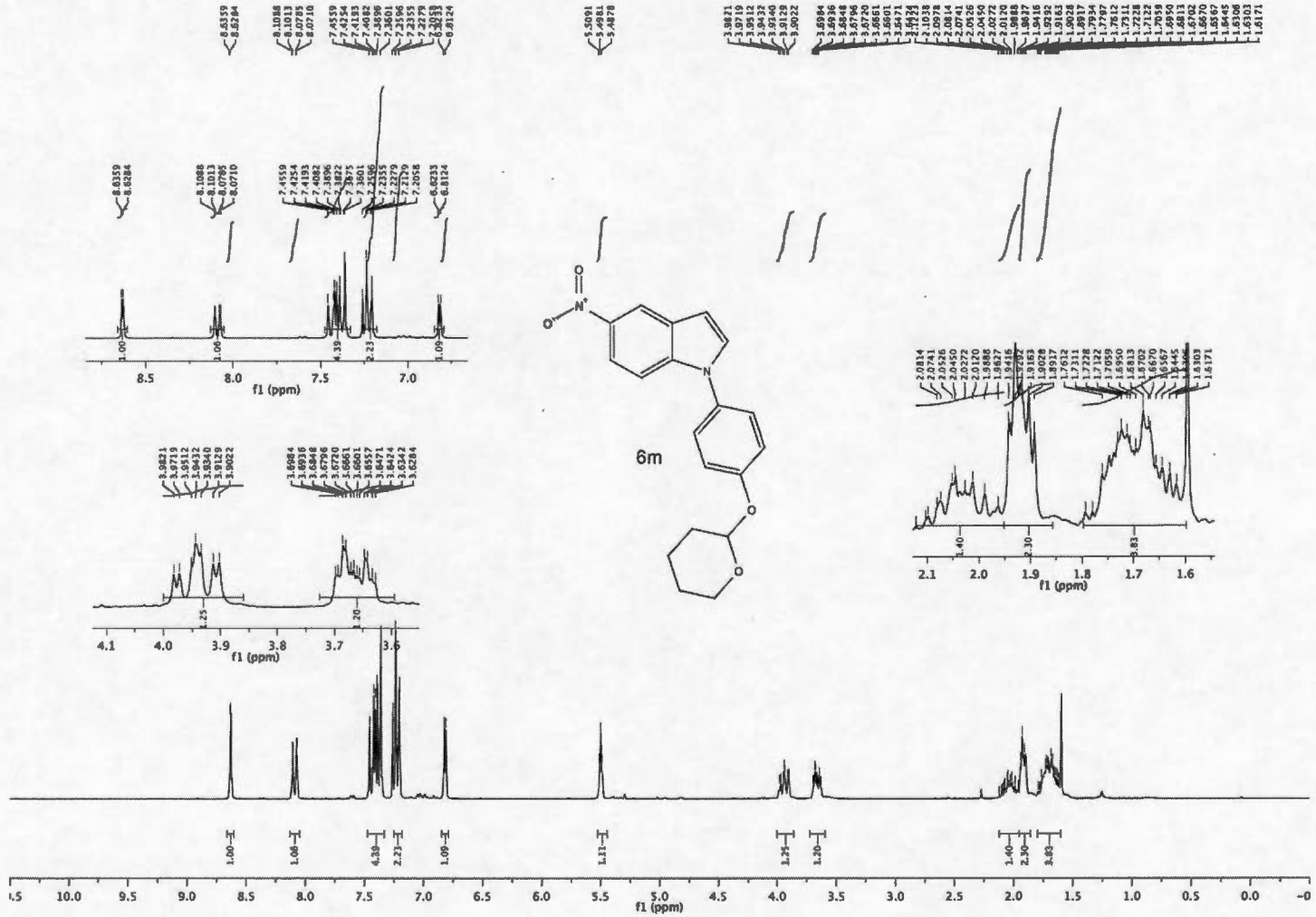

14.3703
60.8007
84.0716
103.2687
112.3384
119.0887
123.5218
123.8098
126.3686
128.5286
130.0938
130.3509
130.9346
131.1895
134.9709
136.3103
139.9598
143.2970
166.4403
6k
f1 (ppm)

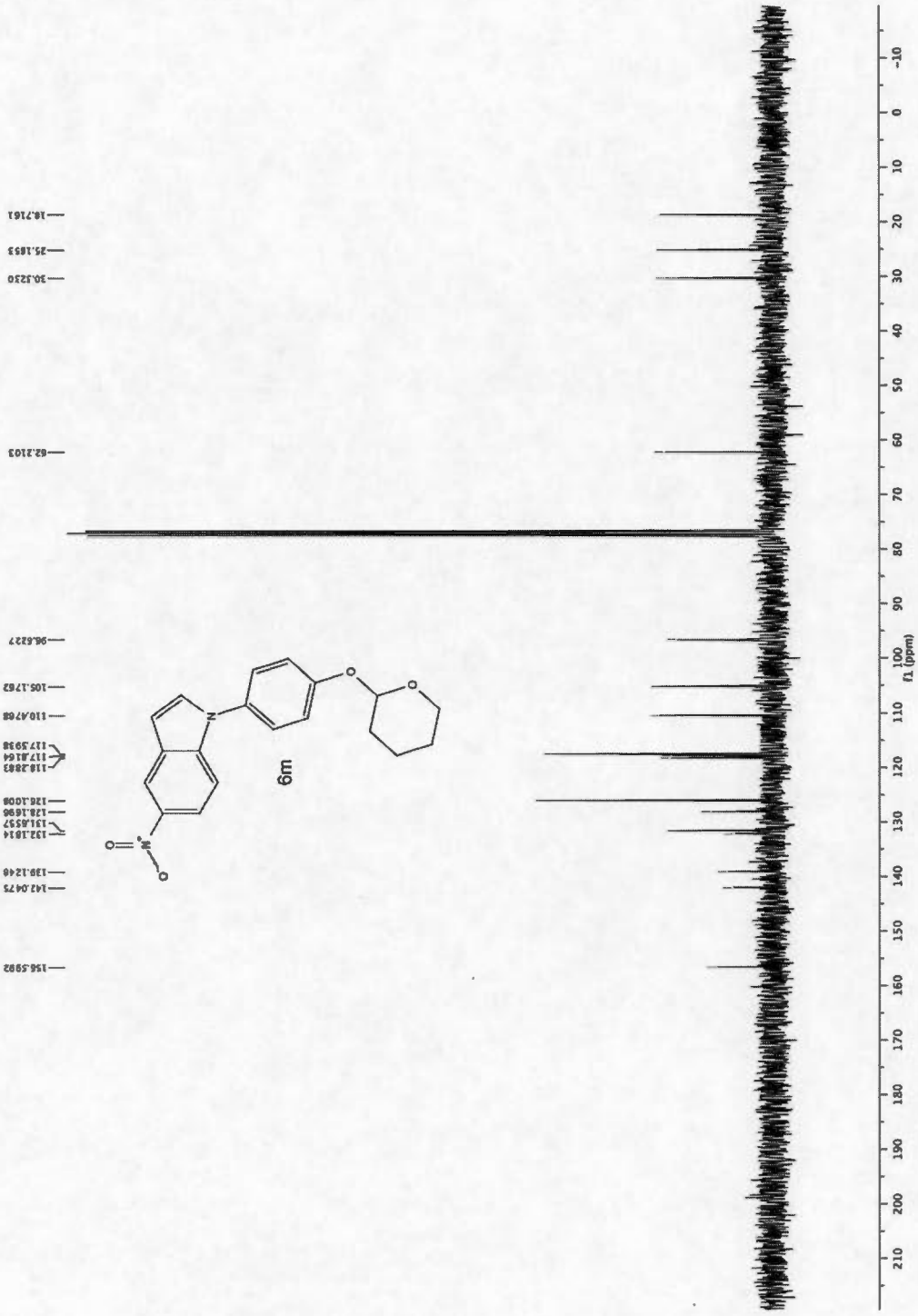

%Transmission
Nombre d'onde (cm-1)
6k
2978,24
3056,84
1705,54
1638,49
1582,04
1512,02
1487,04
1456,20
1385,54
1305,58
1275,10
1231,58
1176,53
1114,07
1033,04
978,94
861,58
790,79
755,34
717,59
774,97
734,34
685,12

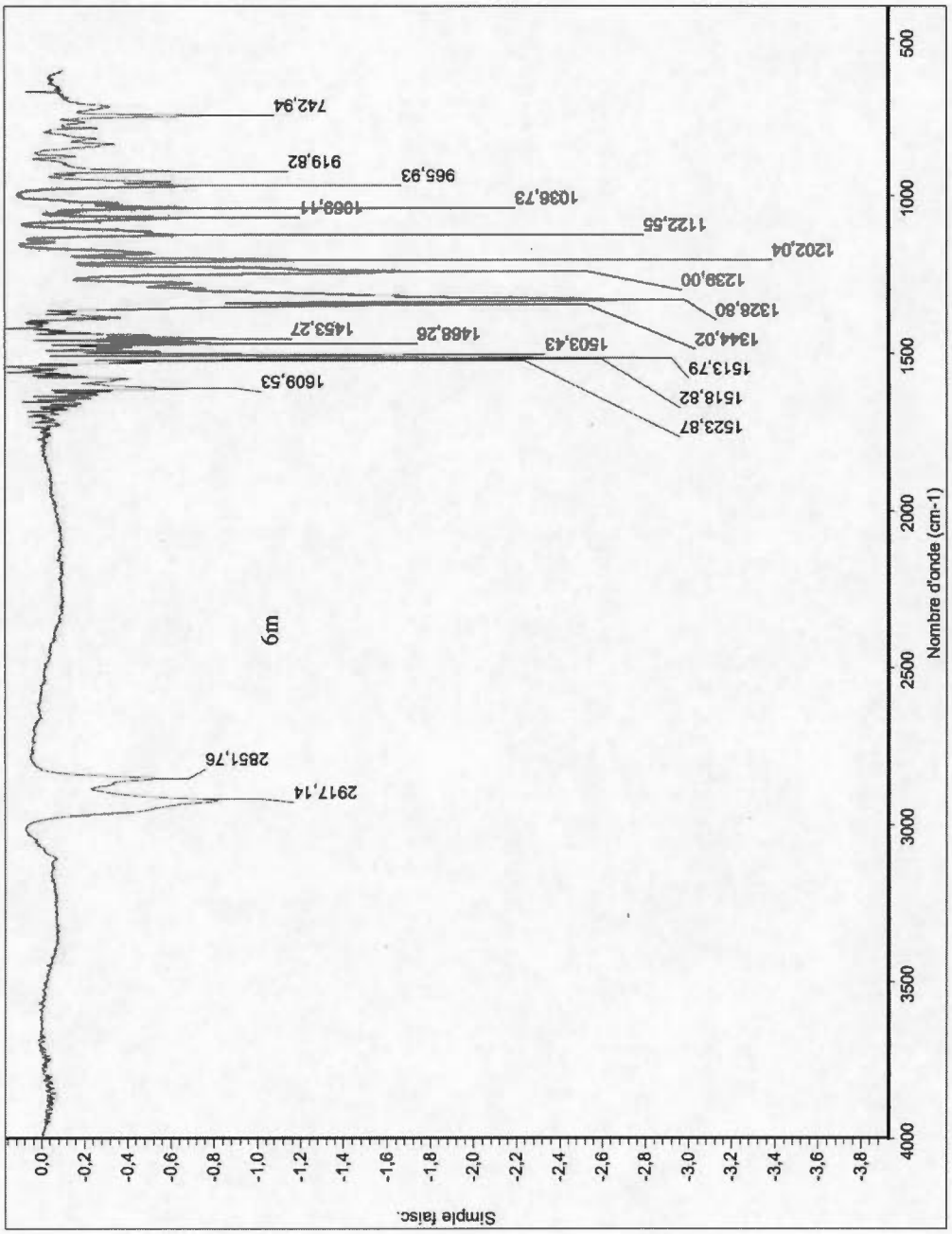

6i
f1 (ppm)

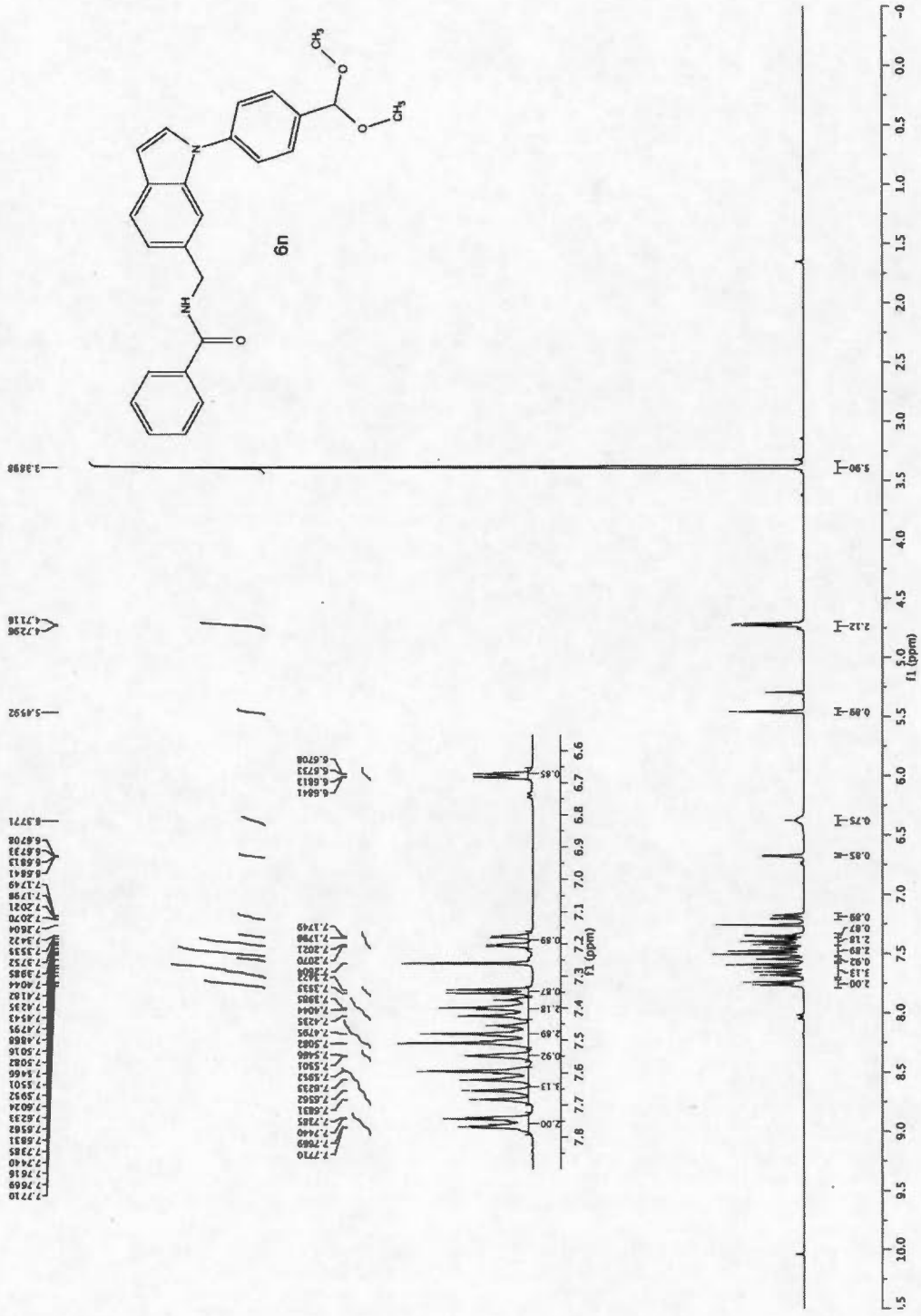

21.1197
22.1824
72.8719
103.4923
110.3186
118.4841
119.5562
124.2060
128.5185
128.9936
130.2271
134.9414
136.3147
137.3606
141.3430
f1 (ppm)
6i

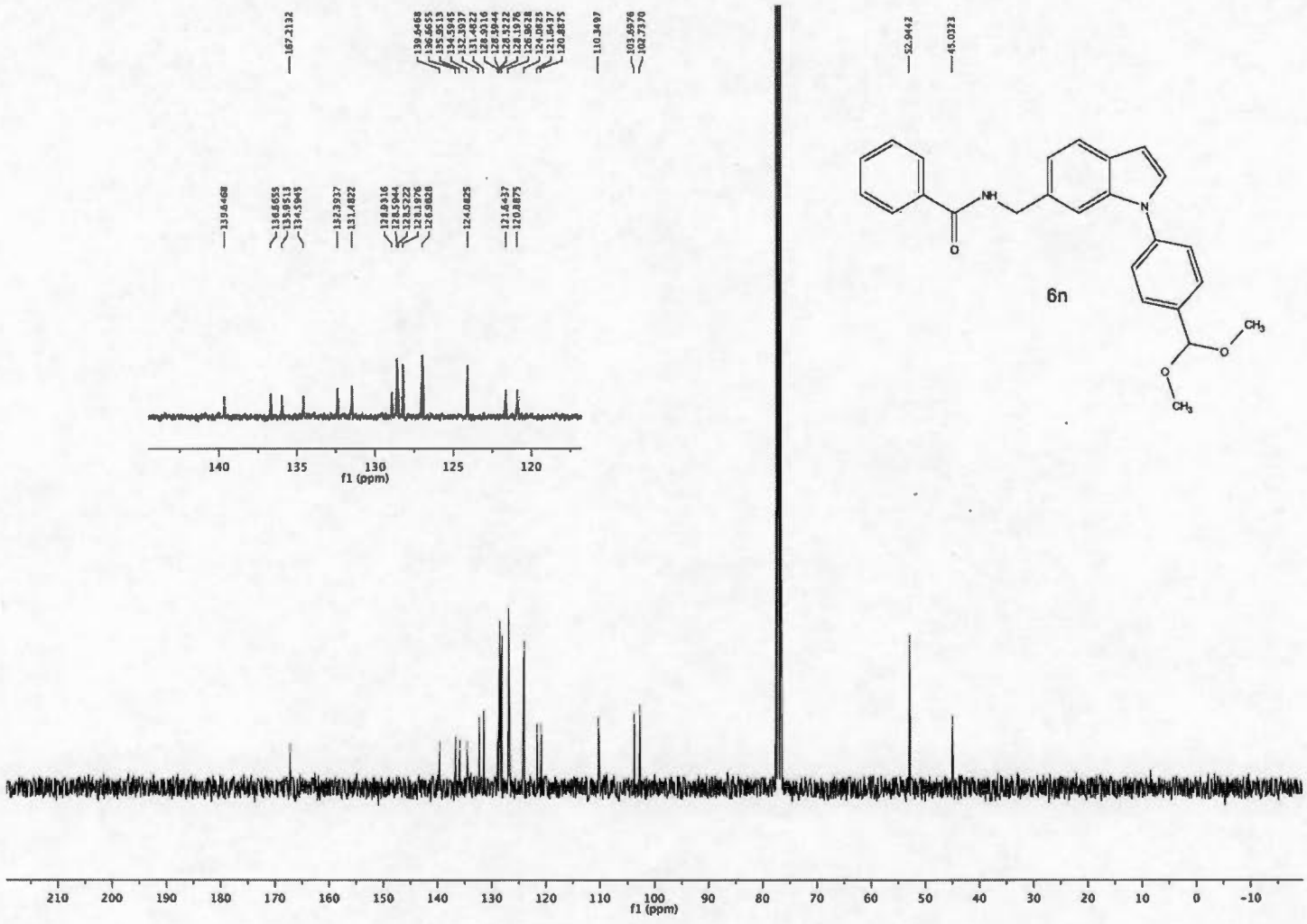

%Transmission
Nombre d'onde (cm-1)
4000
3500
3000
2500
2000
1500
1000
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
3405,68
2971,09
2923,35
1517,88
1474,62
1438,71
1371,50
1333,67
1289,48
1228,06
1108,83
955,88
821,10
805,21
718,40
19

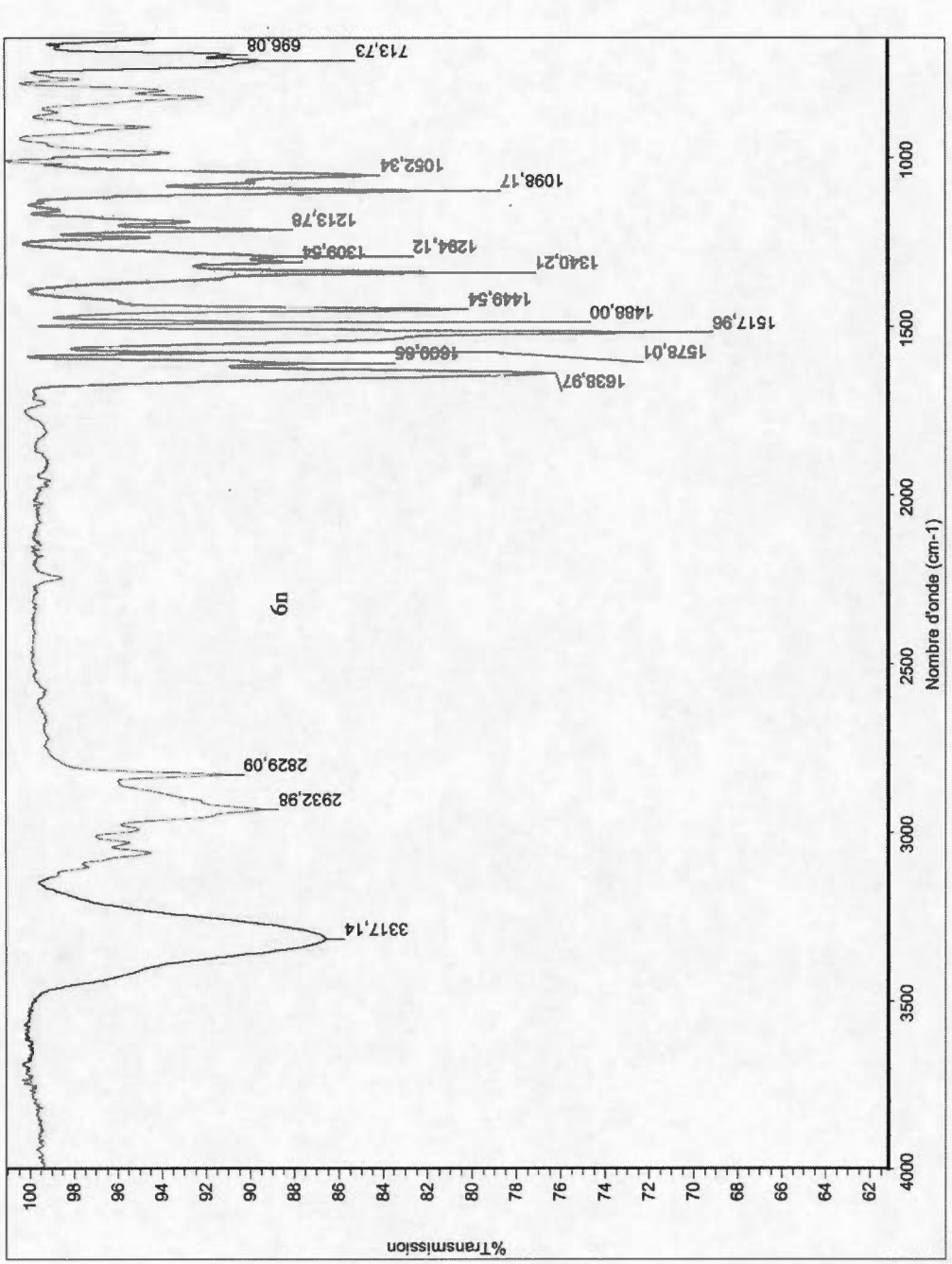

6m
f1 (ppm)

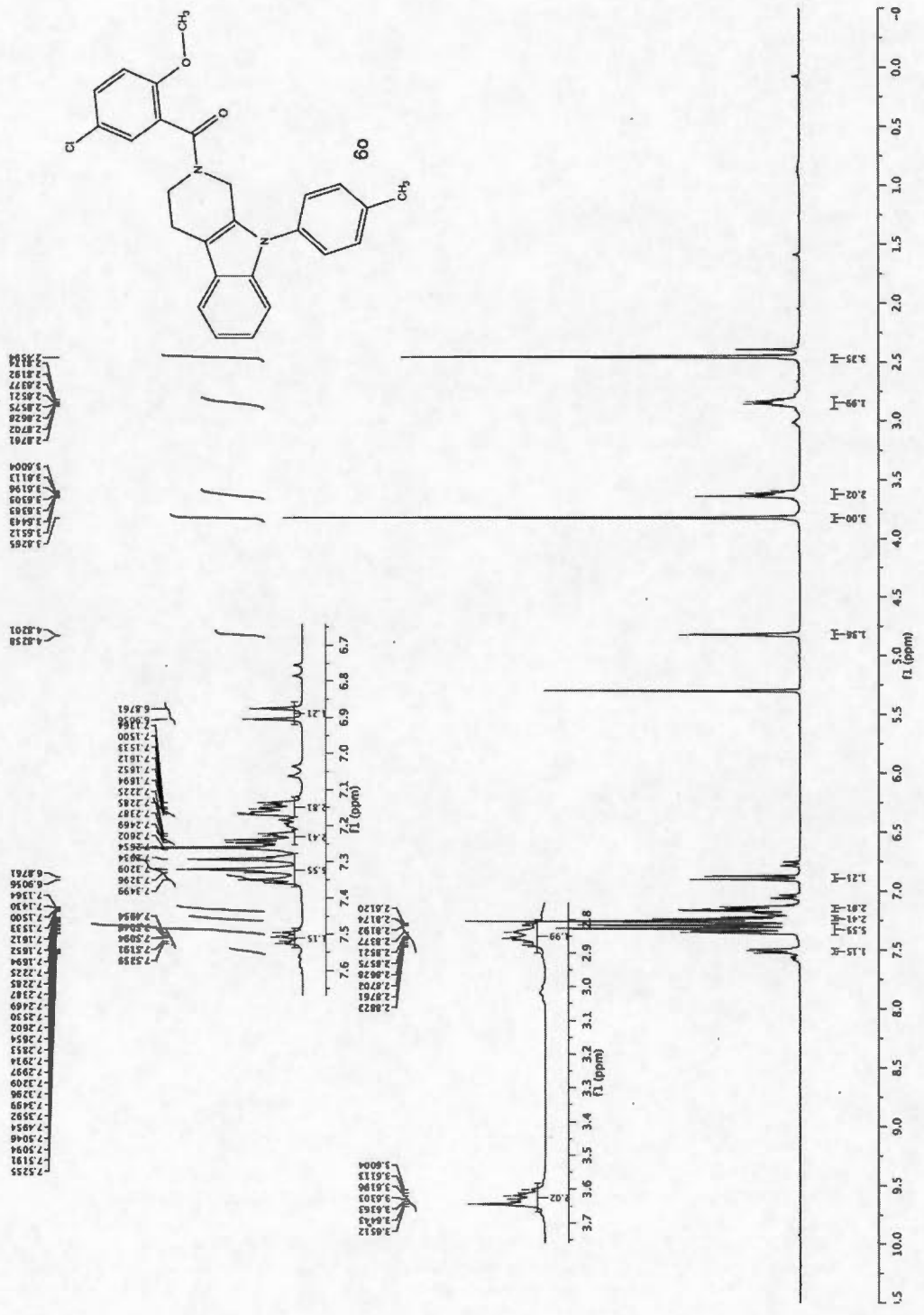

18.7161
25.1853
30.3250
62.2103
96.6227
105.1762
110.4768
118.3883
117.8164
117.5938
128.1696
131.4557
132.1814
138.1246
142.0475
156.5982
6m
f1 (ppm)

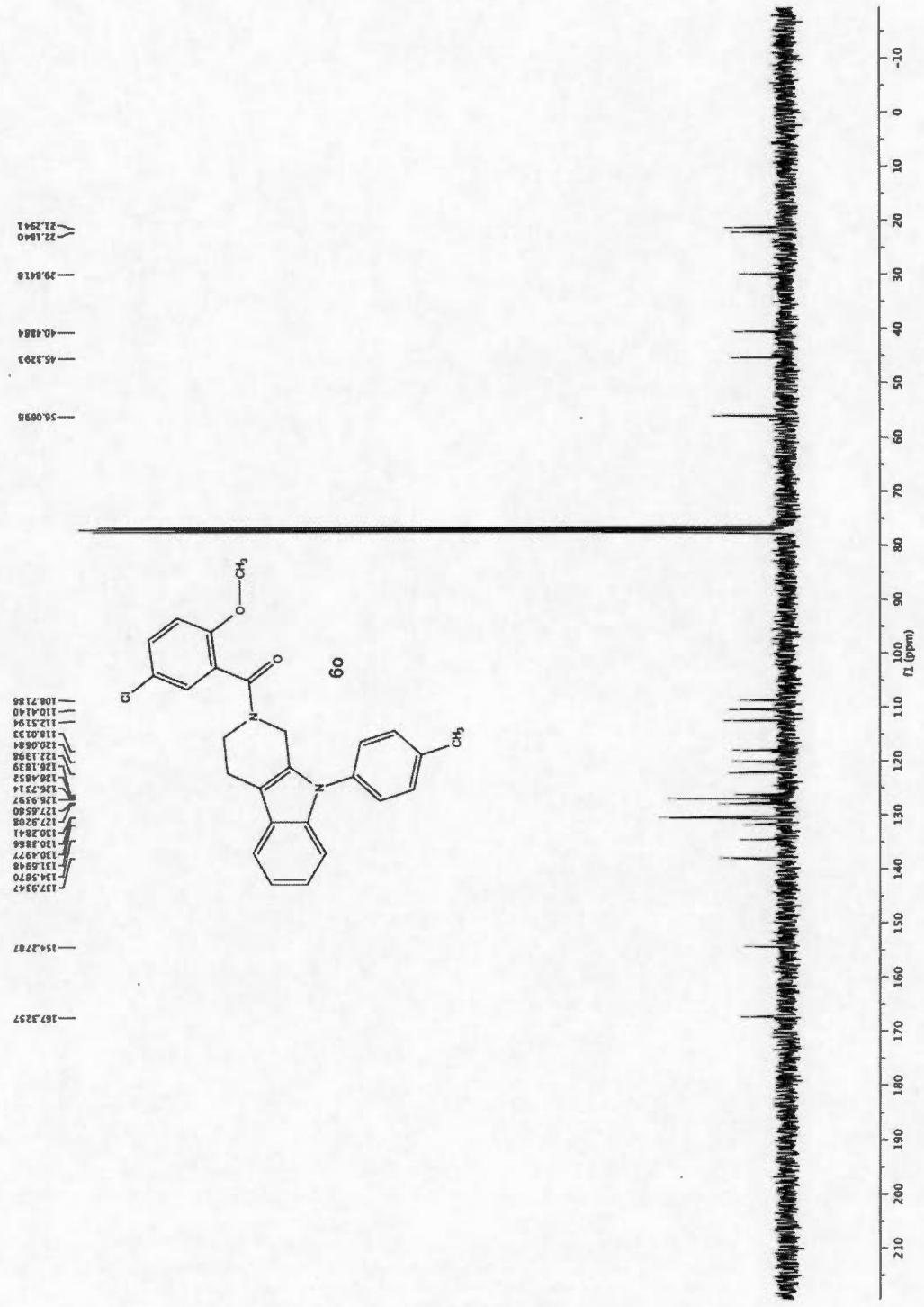

Simple faisc.
0,0
-0,2
-0,4
-0,6
-0,8
-1,0
-1,2
-1,4
-1,6
-1,8
-2,0
-2,2
-2,4
-2,6
-2,8
-3,0
-3,2
-3,4
-3,6
-3,8
4000
3500
3000
2500
2000
1500
1000
500
Nombre d'onde (cm-1)
6m
2917,14
2851,76
1609,53
1523,87
1518,82
1513,79
1503,43
1468,26
1453,27
1344,02
1328,80
1238,00
1202,04
1122,55
1068,11
1036,73
965,93
919,82
742,94

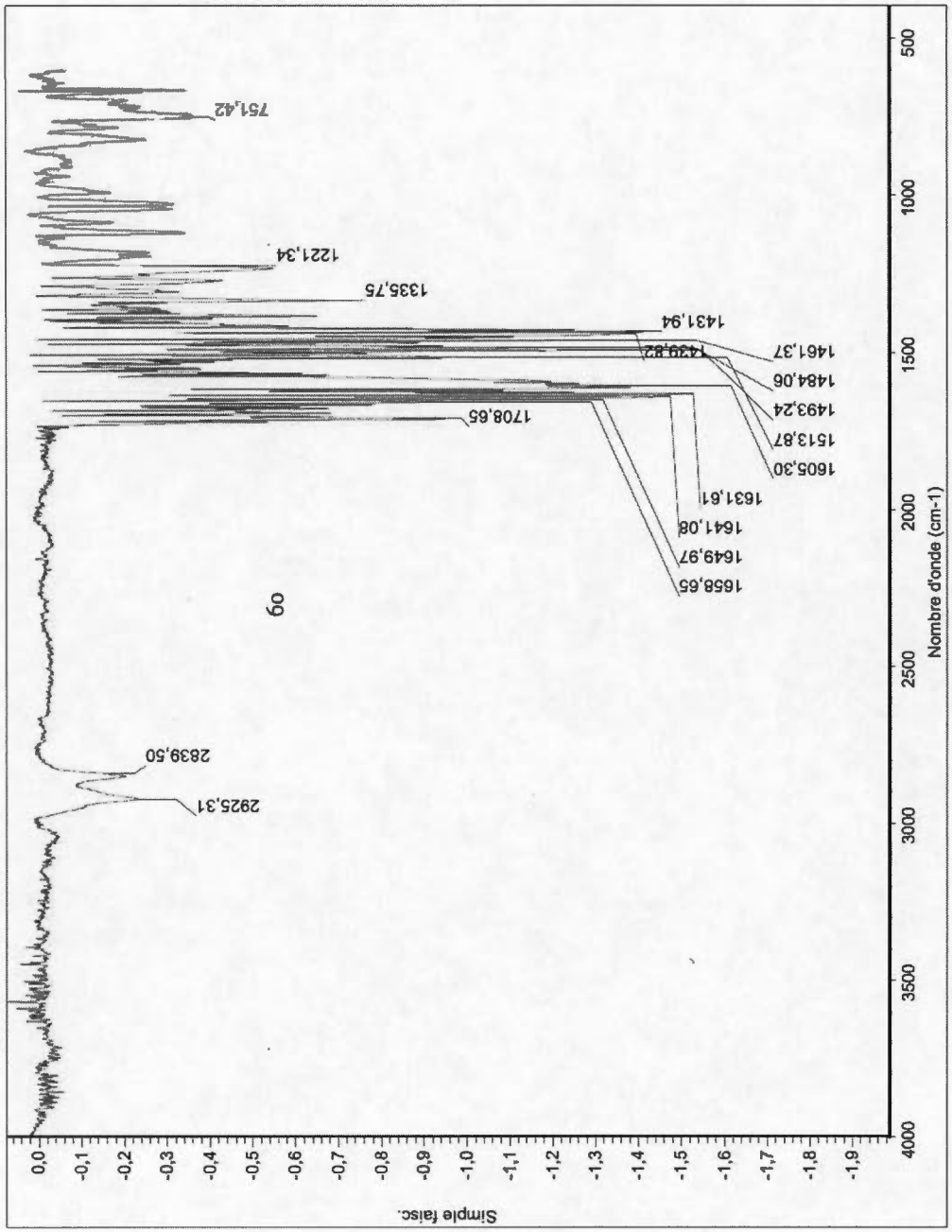

6n
f1 (ppm)

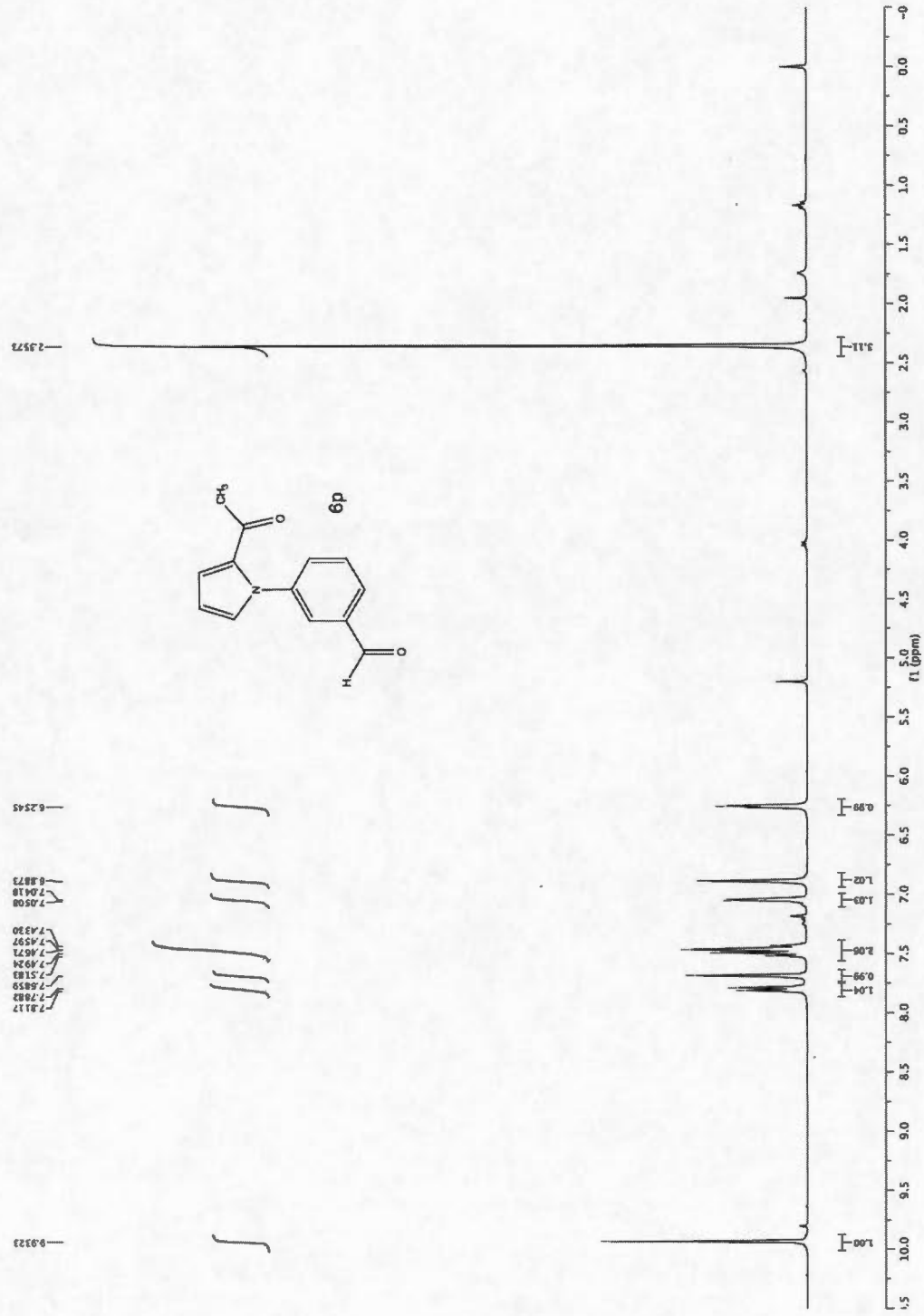

167.2132
139.6468
136.6655
135.5513
134.5945
131.3937
131.4822
128.9316
128.5944
128.5222
128.1976
126.9828
124.0825
121.4437
120.8875
110.3497
103.6976
102.7370
52.9442
45.0323
6n
NH
O
N
O
O
CH3
CH3
f1 (ppm)
f1 (ppm)

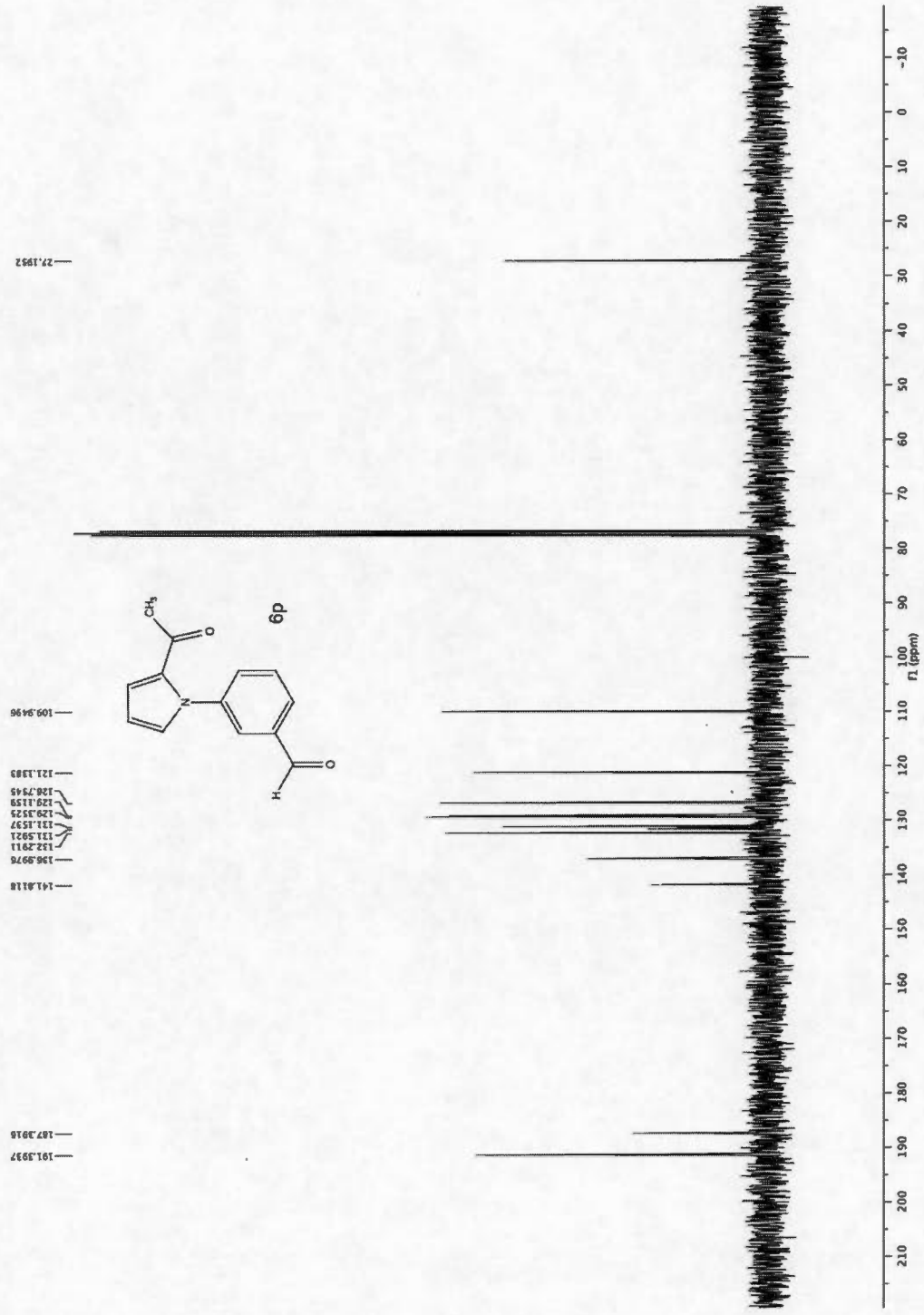

%Transmission
Nombre d'onde (cm-1)
4000
3500
3000
2500
2000
1500
1000
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64
62
3317,14
2932,98
2829,09
1638,97
1578,01
1517,96
1488,00
1449,54
1340,21
1309,54
1284,12
1213,78
1098,17
1052,34
713,73
696,08

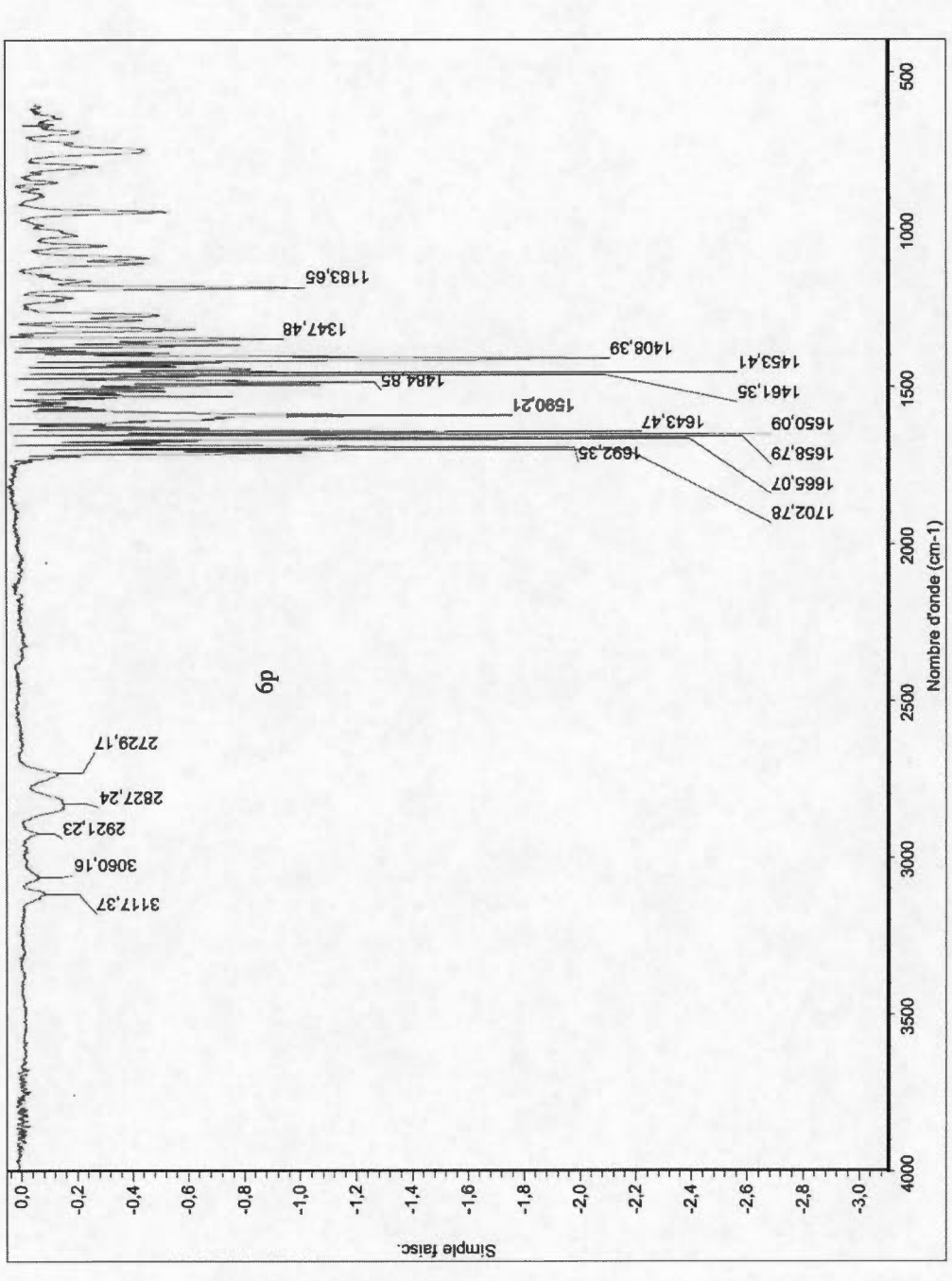

60
f1 (ppm)


60
f1 (ppm)


Simple faisc.
Nombre d'onde (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
0,0
-0,1
-0,2
-0,3
-0,4
-0,5
-0,6
-0,7
-0,8
-0,9
-1,0
-1,1
-1,2
-1,3
-1,4
-1,5
-1,6
-1,7
-1,8
-1,9
2925,31
2839,50
1708,65
1658,65
1649,97
1641,08
1631,61
1605,30
1513,87
1493,24
1484,06
1461,37
1431,94
1429,82
1335,75
1221,34
751,42
09


6p
f1 (ppm)


6p
27.1952
109.5496
121.1383
128.7945
129.1159
129.3525
131.1597
131.5921
132.2911
136.8976
141.8118
187.3918
191.3937
f1 (ppm)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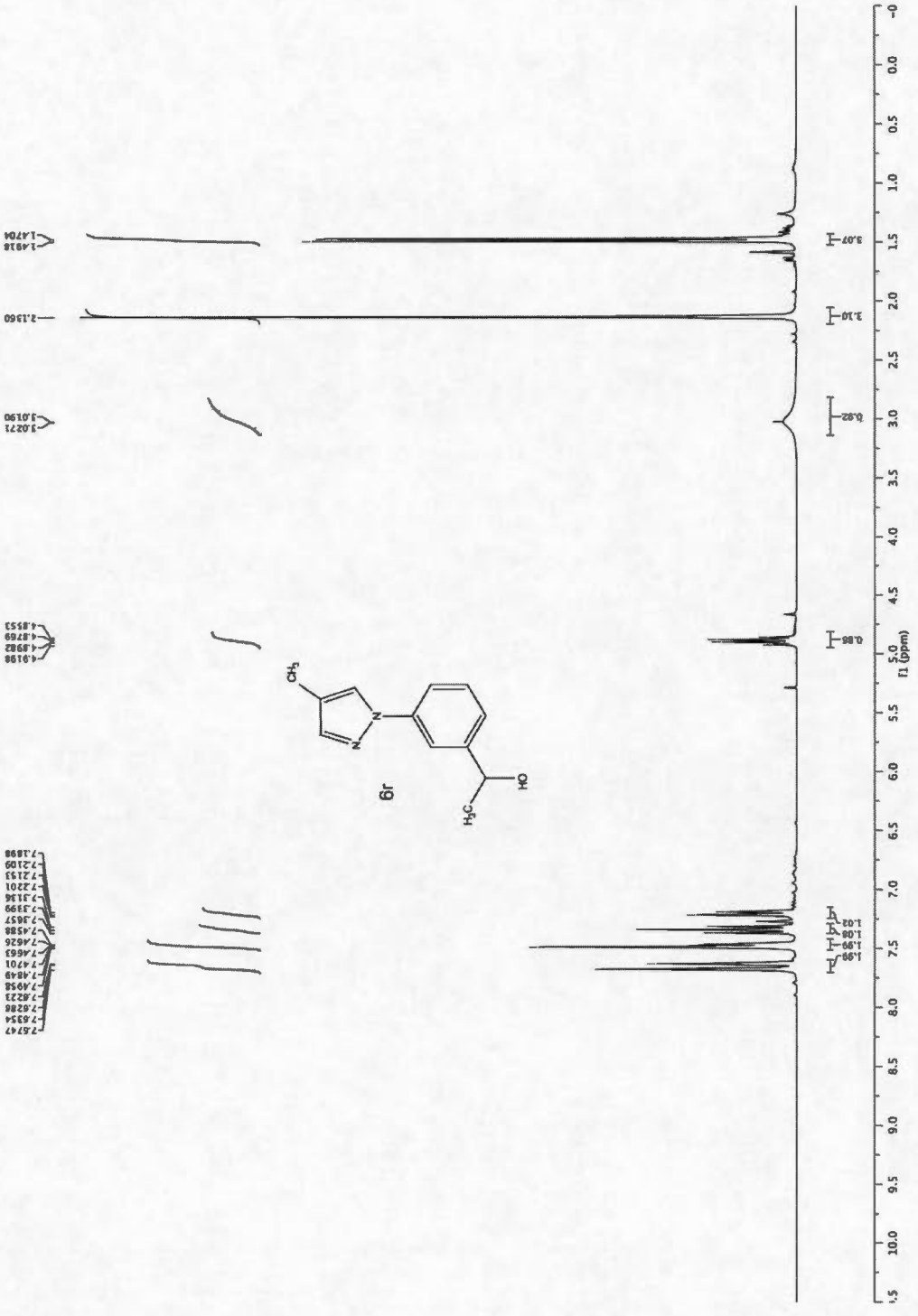
-0,6
-0,8
-1,0
-1,2
-1,4
-1,6
-1,8
-2,0
-2,2
-2,4
-2,6
-2,8
-3,0
4000
3500
3000
2500
2000
1500
1000
500
Nombre d'onde (cm-1)
3117,37
3060,16
2921,23
2827,24
2729,17
1702,78
1665,07
1658,79
1650,09
1643,47
1592,35
1580,21
1484,85
1461,35
1453,41
1408,39
1347,48
1183,65
6p

6q
f1 (ppm)


6r
OH
CH3
f1 (ppm)

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69.8919
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117.6069
115.9268
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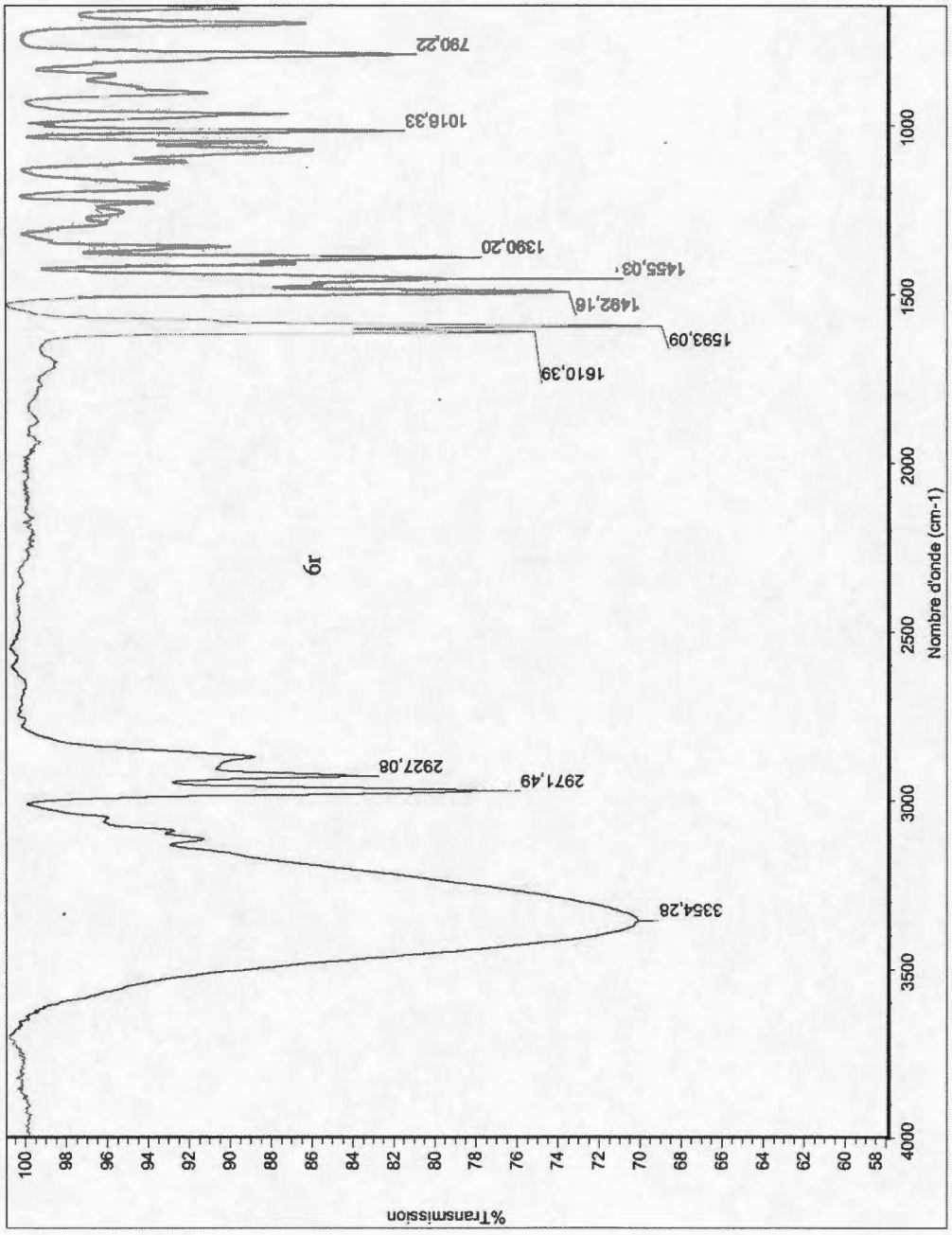
129.0463
140.3576
141.7591
147.7775
6g
OH
H3C
CH3
f1 (ppm)


%Transmission
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2927,08
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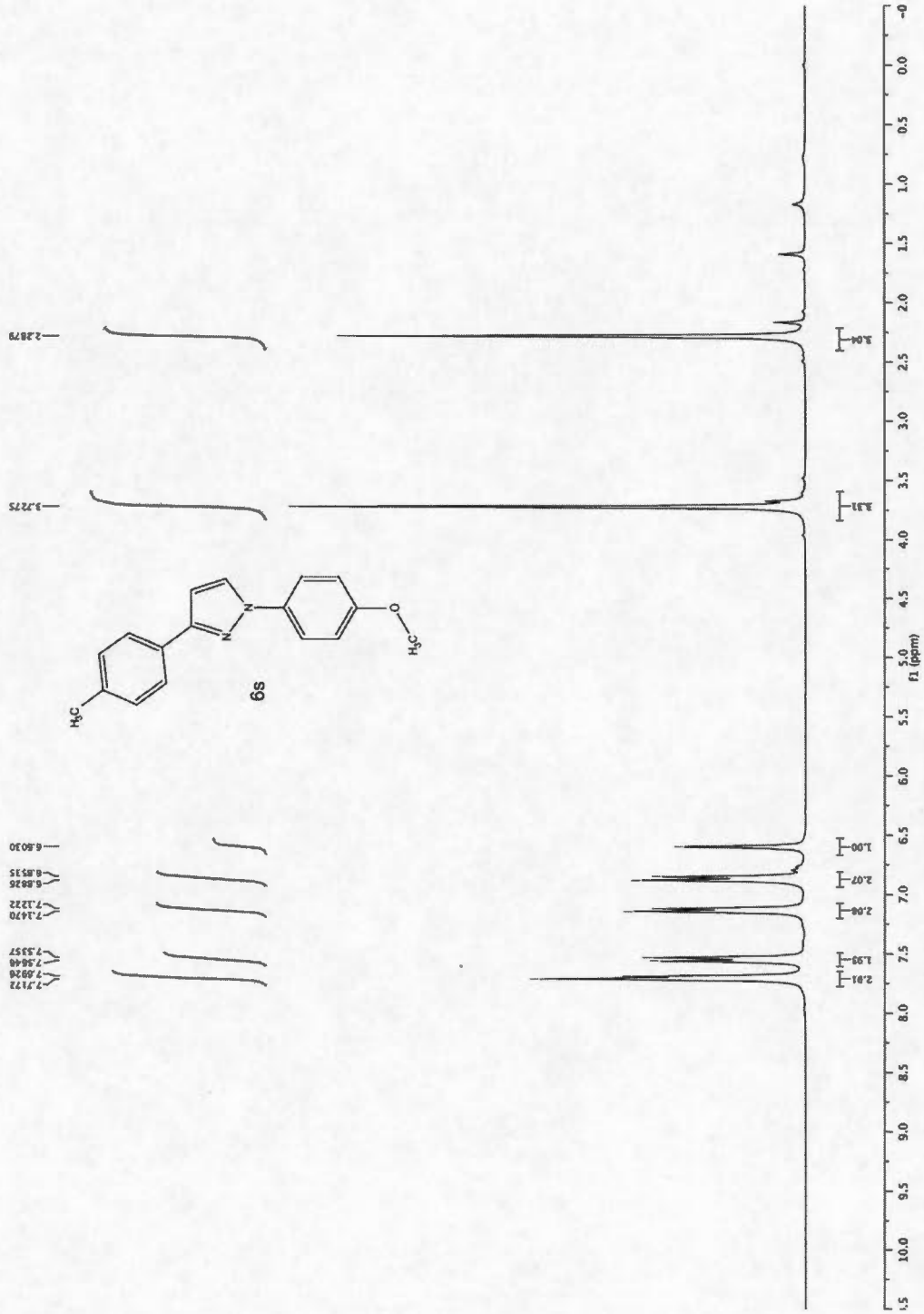
1593,09
1482,16
1455,03
1390,20
1018,33
780,22
6r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3.8275
6.8030
6.8535
6.8682
7.1470
7.1722
7.3557
7.3846
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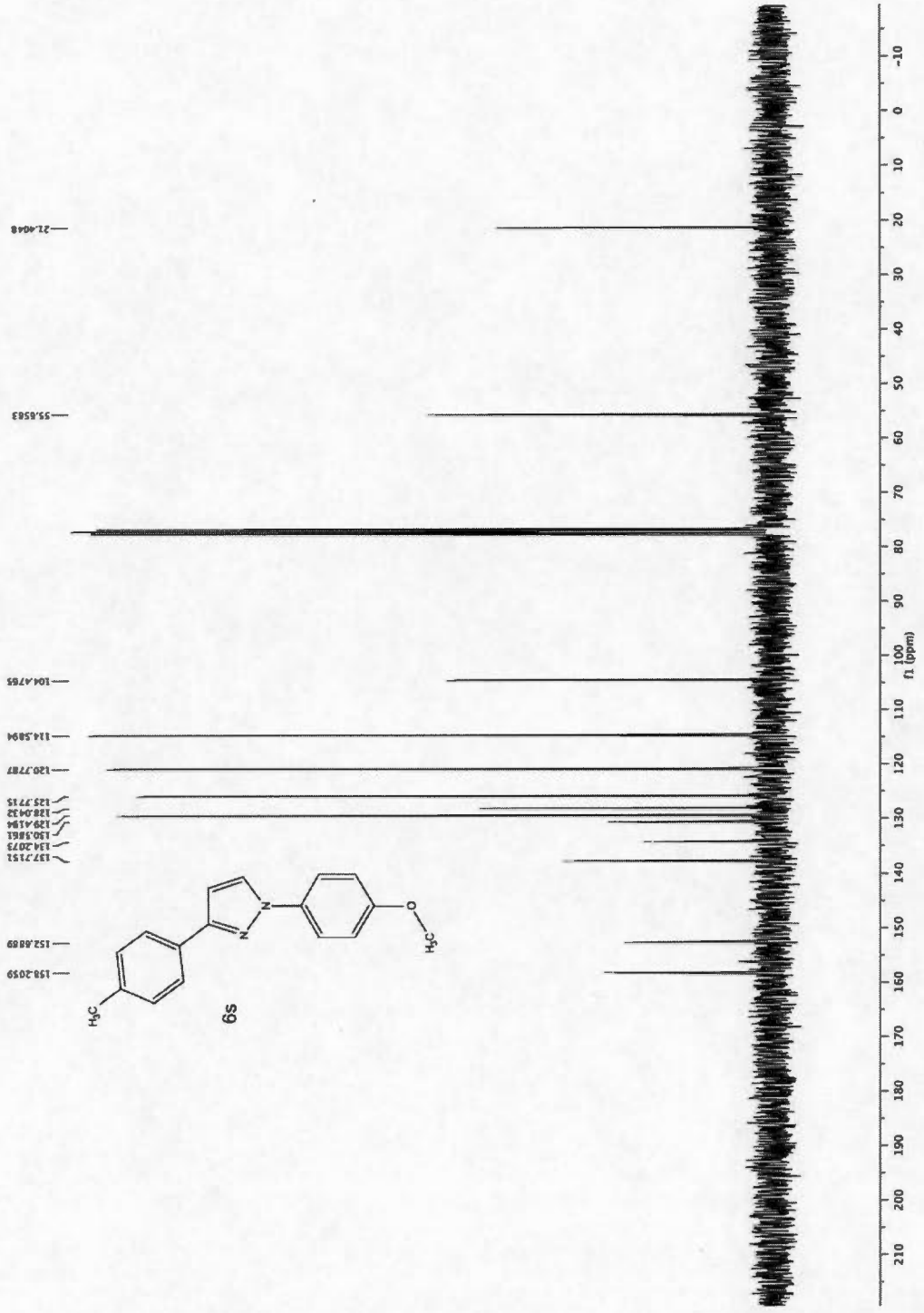
2.06
1.99
2.01
6s
f1 (ppm)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104.4765
114.5894
120.7787
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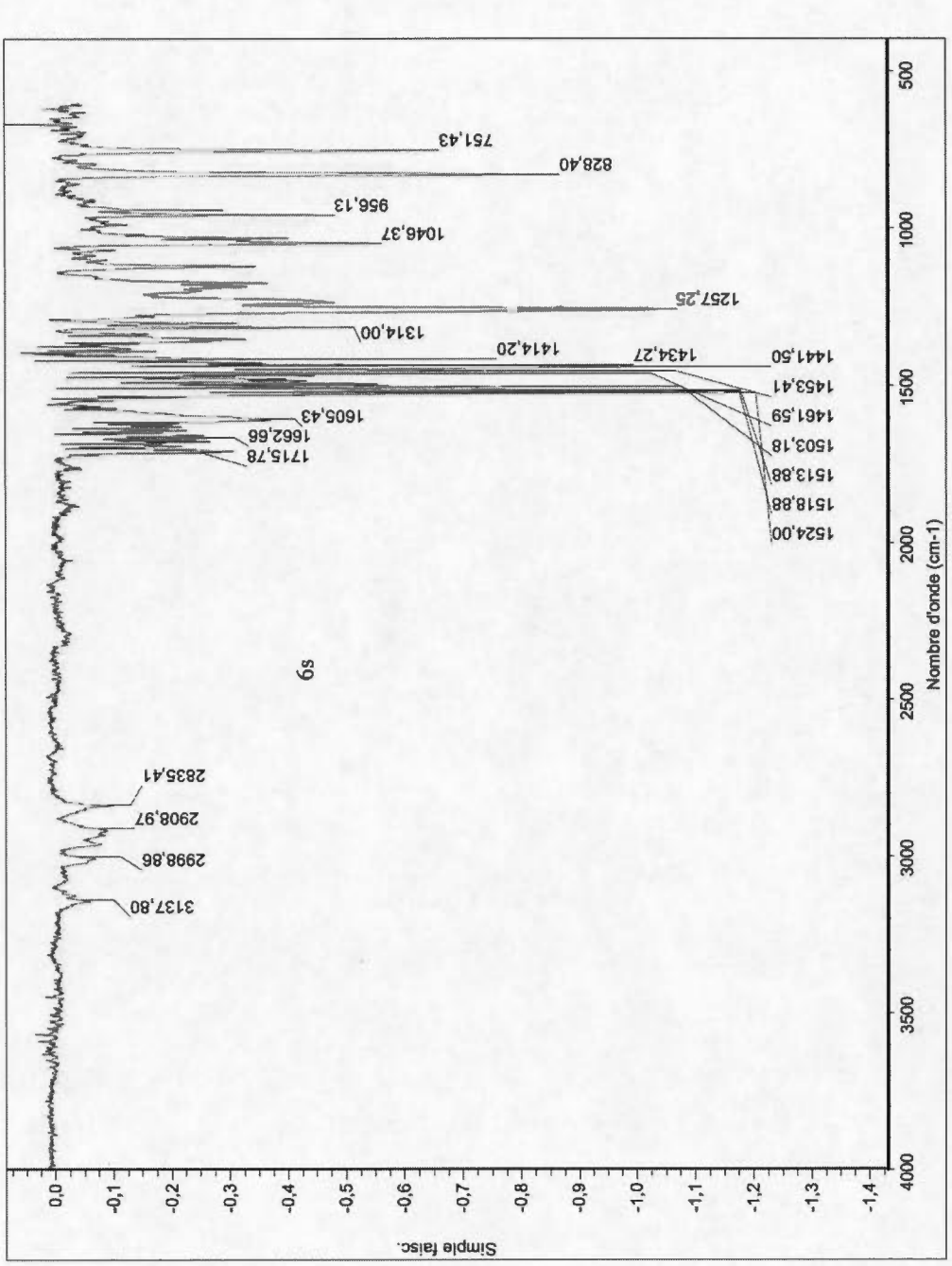
128.0432
129.4196
130.3861
134.2079
137.7151
152.8889
158.2059
6s
f1 (ppm)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-0,9
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-1,1
-1,2
-1,3
-1,4
4000
3500
3000
2500
2000
1500
1000
500
Nombre d'onde (cm-1)
sg
3137,80
2998,86
2908,97
2835,41
1715,78
1662,66
1605,43
1524,00
1518,88
1513,88
1503,18
1461,59
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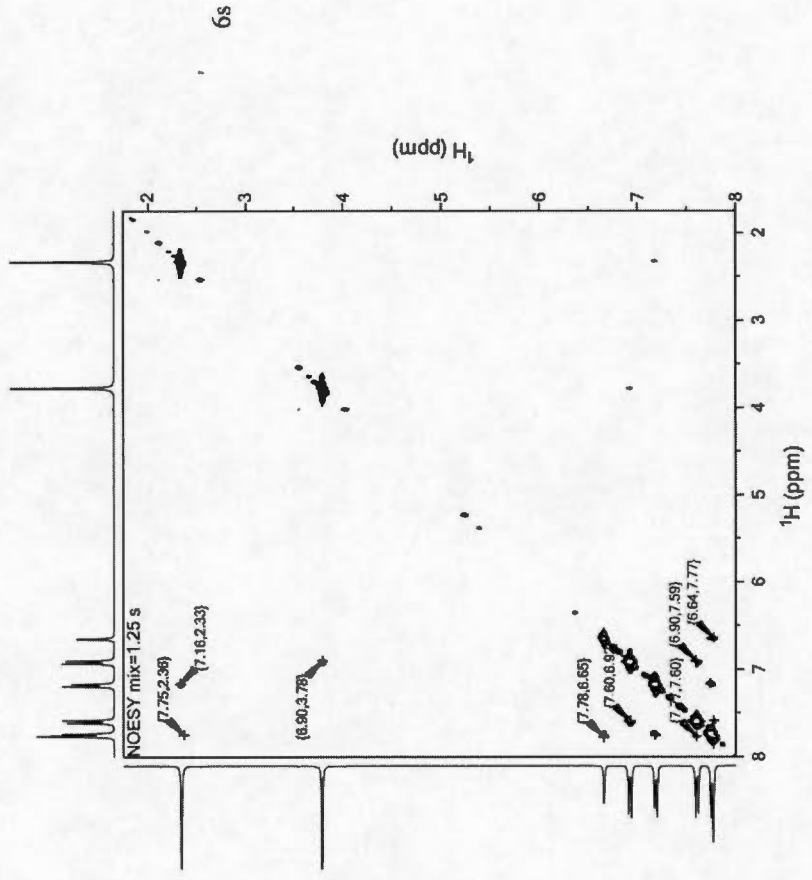
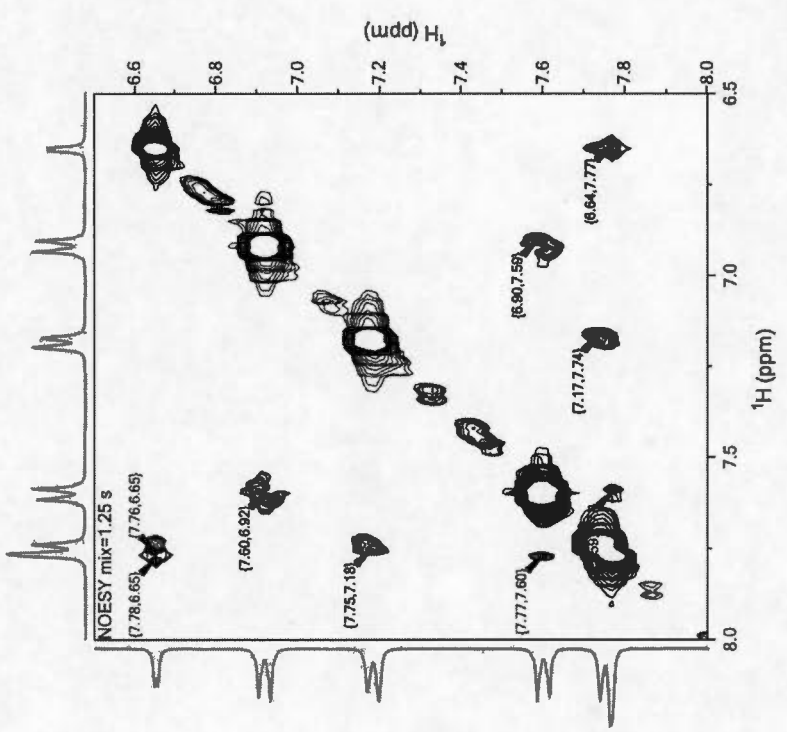
1257,25
1046,37
956,13
828,40
751,43


sq
NOESY mix=1.25 s
(7.75,2.36)
(7.16,2.33)
(8.90,3.78)
(7.78,6.65)
(7.60,6.9
(7.7,7.60)
(6.90,7.59)
(6.64,7.77)
^{1}H (ppm)
^{1}H (ppm)


NOESY mix=1.25 s
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(7.76,6.65)
(7.60,6.92)
(7.75,7.18)
(7.77,7.60)
(6.90,7.59)
(7.17,7.74)
(6.64,7.77)
^{1}H (ppm)
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7.5
7.0
6.5
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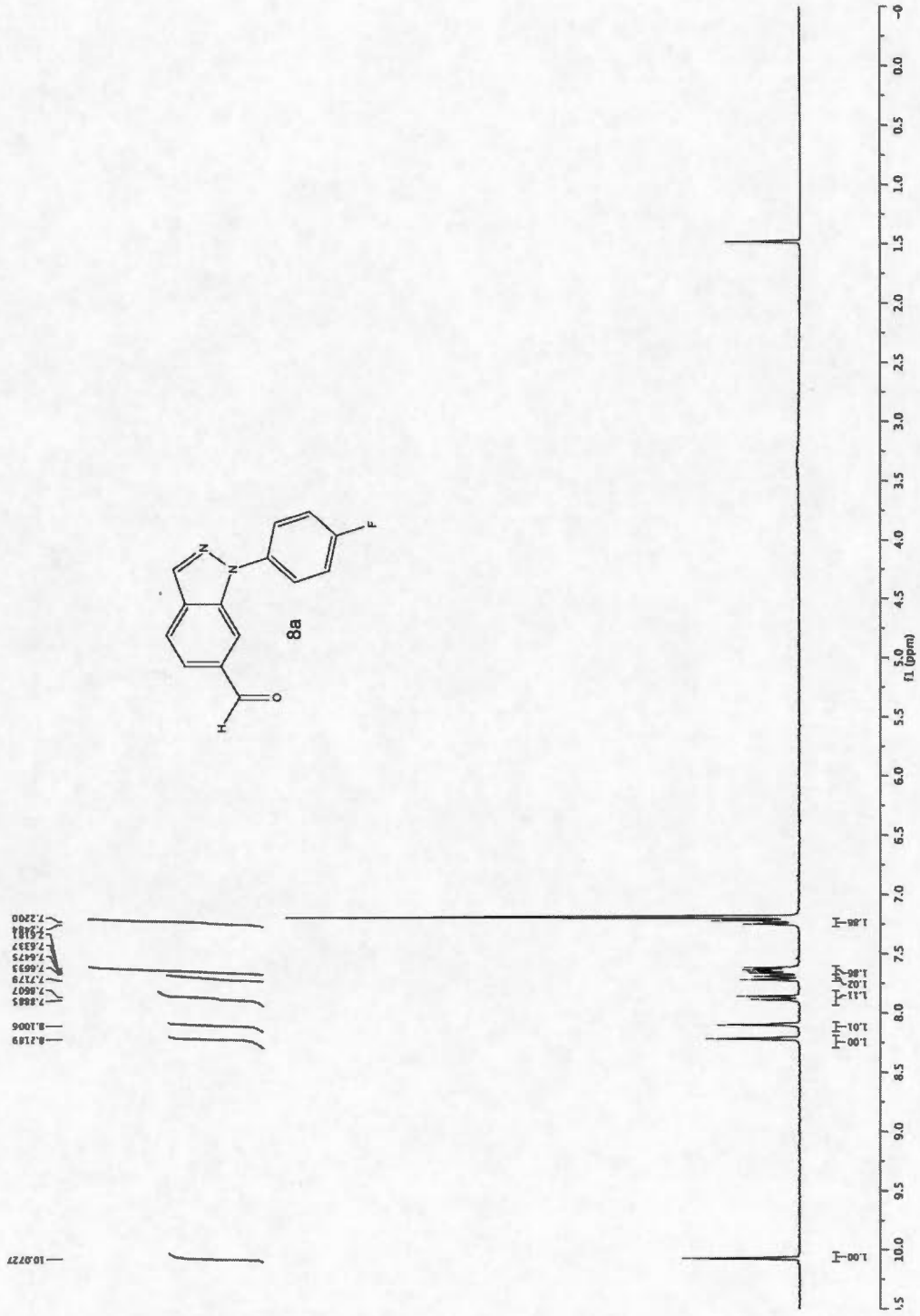
6.8
7.0
7.2
7.4
7.6
7.8

δs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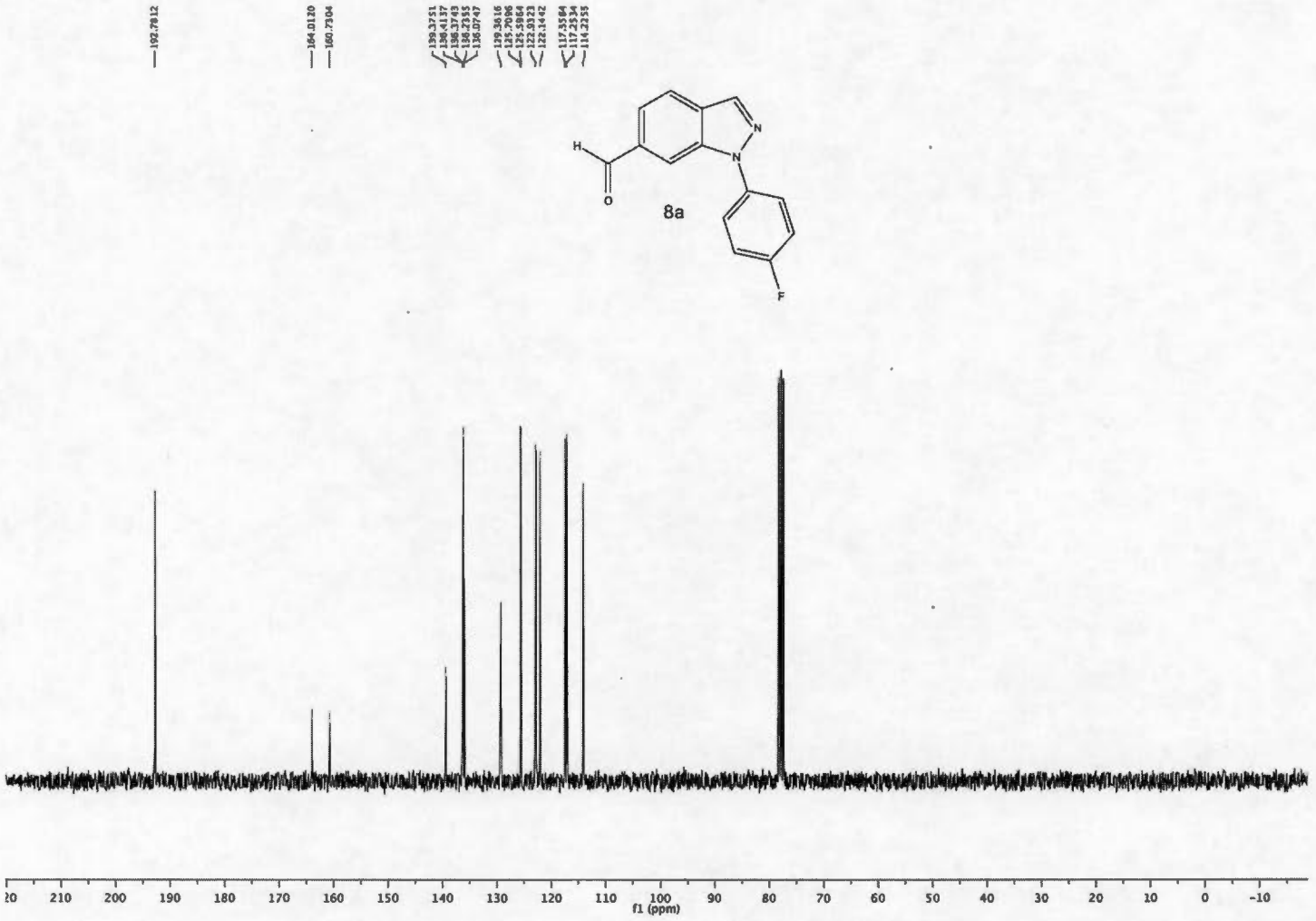
8.2189
8.1006
7.8865
7.8607
7.7179
7.6633
7.6475
7.6337
7.2200
1.00
1.01
1.00
1.11
1.02
1.86
1.86
f1 (ppm)
8a
F
N
N
O
H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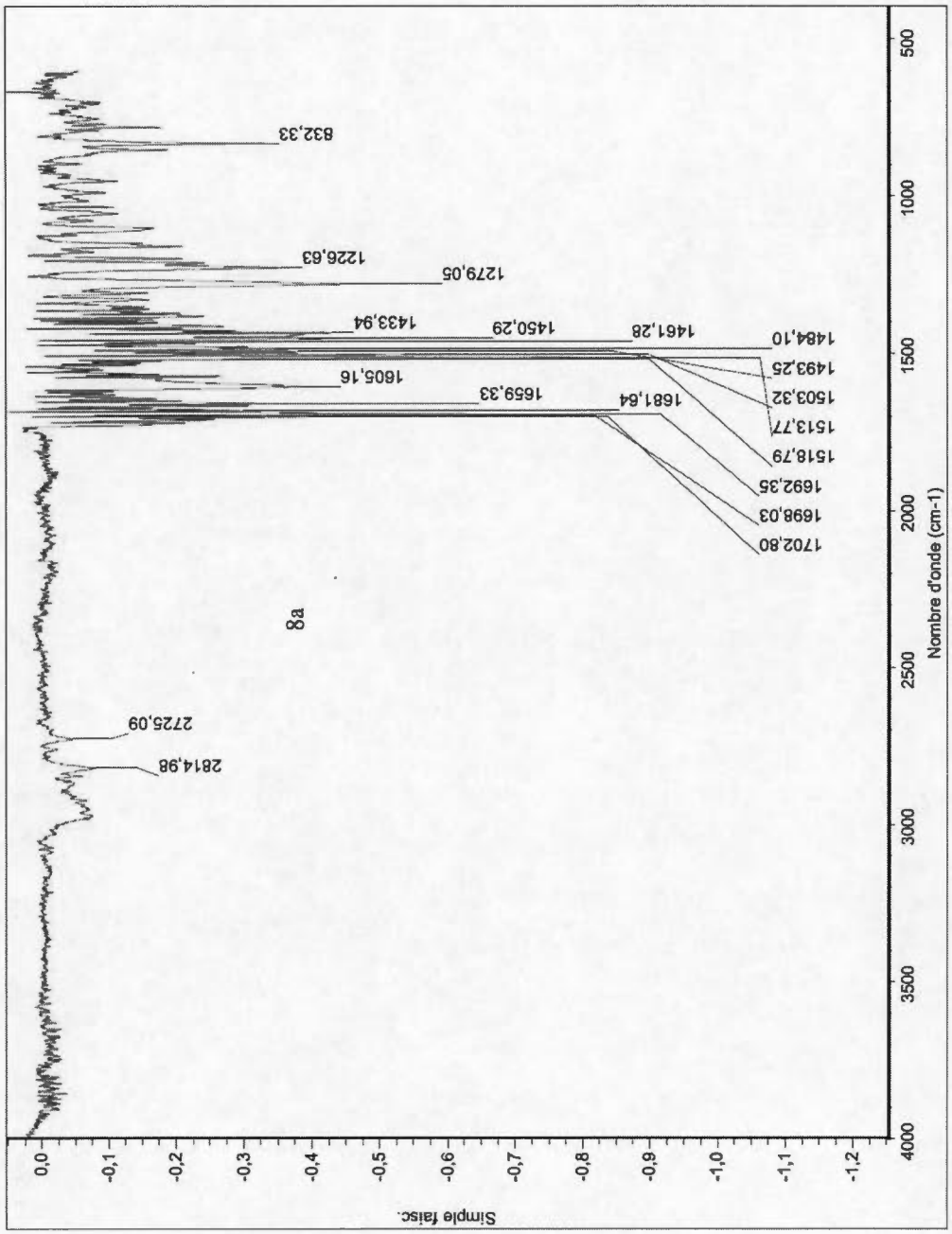
160.7304
139.3751
138.4137
138.3743
138.2515
138.0747
129.3616
125.7096
125.5864
122.0323
122.1442
117.3584
117.2334
114.2255
H
O
N
N
F
8a
f1 (ppm)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-0,9
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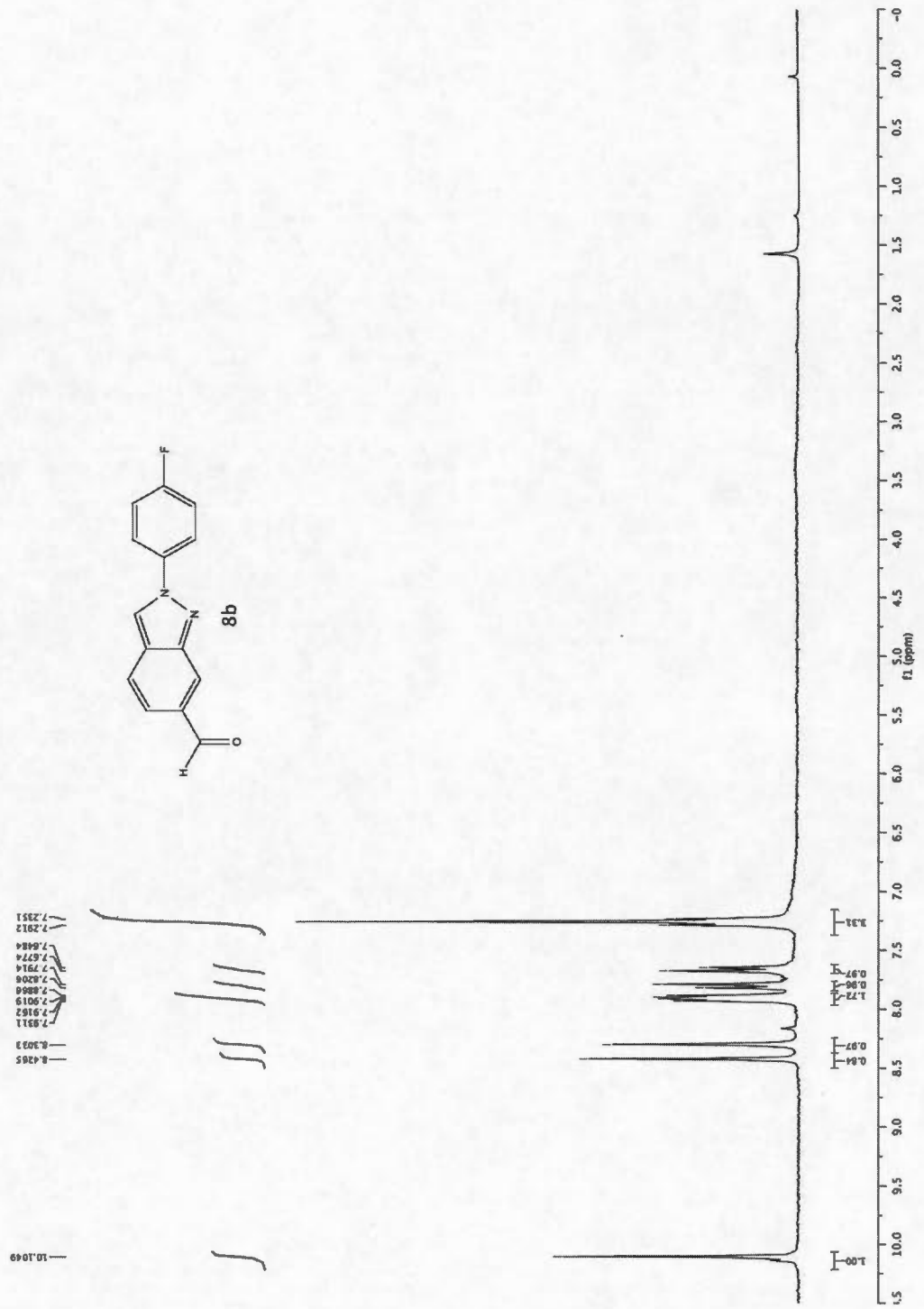
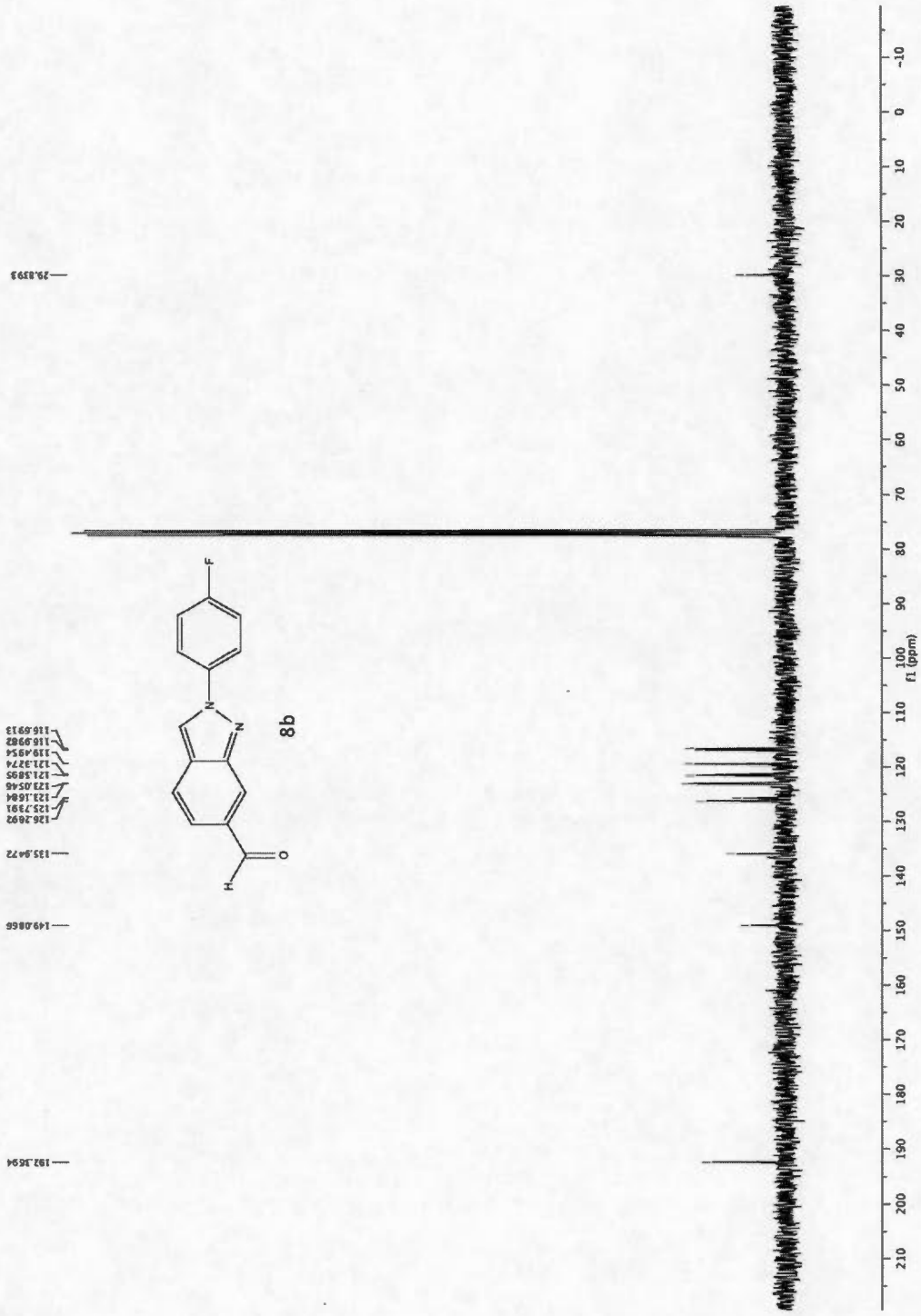
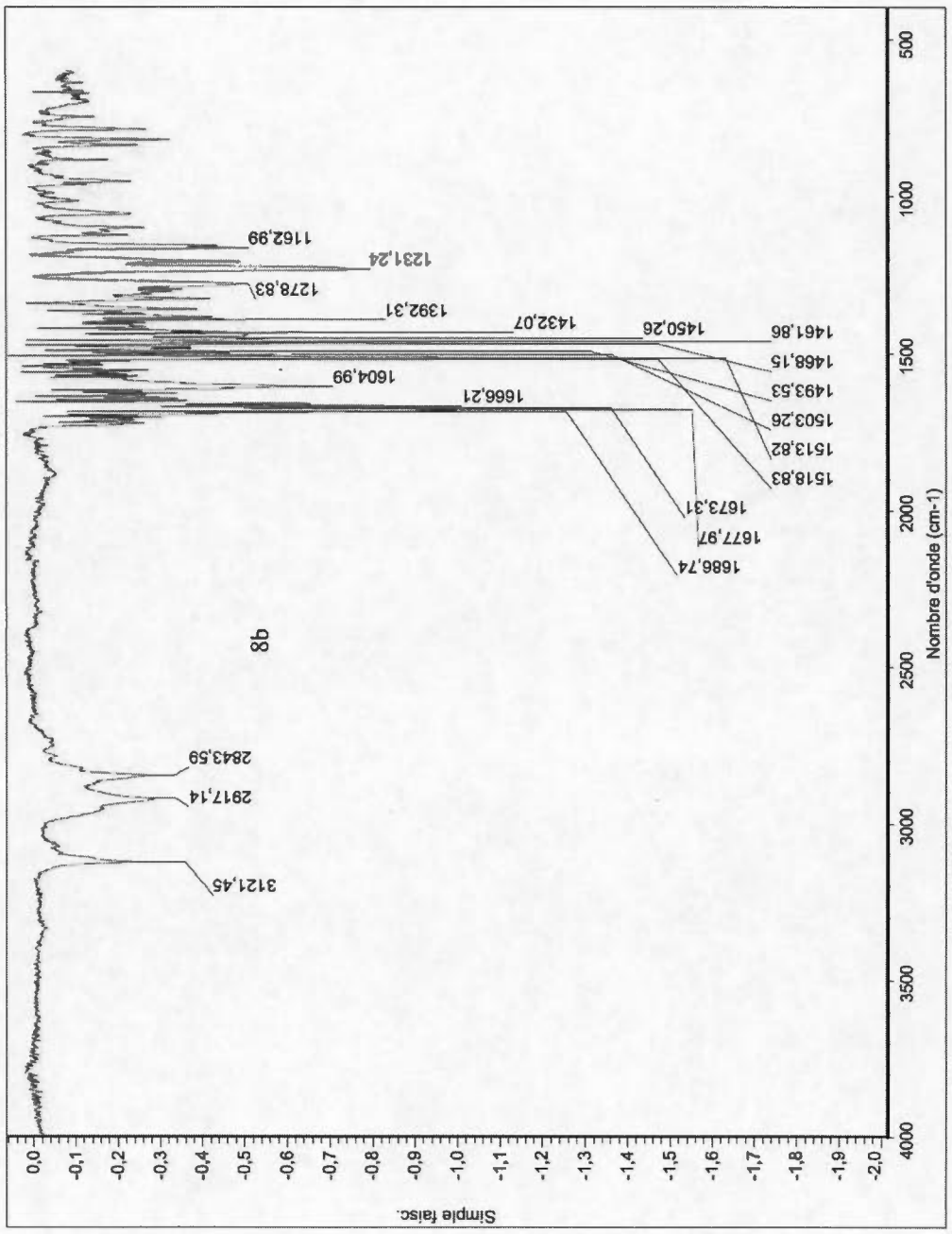
-1,1
-1,2
4000
3500
3000
2500
2000
1500
1000
500
Nombre d'onde (cm-1)
8a
2725,09
2814,98
832,33
1226,63
1279,05
1433,94
1450,29
1461,28
1484,10
1493,25
1503,32
1513,77
1518,79
1692,35
1698,03
1702,80
1681,64
1659,33
1605,16


8b
F
N
N
O
H
10.1049
8.4365
8.3033
7.9511
7.9162
7.9019
7.8866
7.8206
7.7914
7.6774
7.6484
7.2951
7.2812
1.00
0.97
0.84
1.73
0.96
0.97
3.31
f1 (ppm)


8b
192.3694
149.0866
135.9472
126.2092
125.7991
123.1684
123.0546
121.3895
121.3274
118.4954
116.8962
116.8913
29.8393
f1 (ppm)


8b
Simple faisc.
Nombre d'onde (cm-1)
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3500
3000
2500
2000
1500
1000
500
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-0,2
-0,3
-0,4
-0,5
-0,6
-0,7
-0,8
-0,9
-1,0
-1,1
-1,2
-1,3
-1,4
-1,5
-1,6
-1,7
-1,8
-1,9
-2,0
3121,45
2917,14
2843,59
1686,74
1677,97
1673,31
1666,21
1604,99
1518,83
1513,82
1503,26
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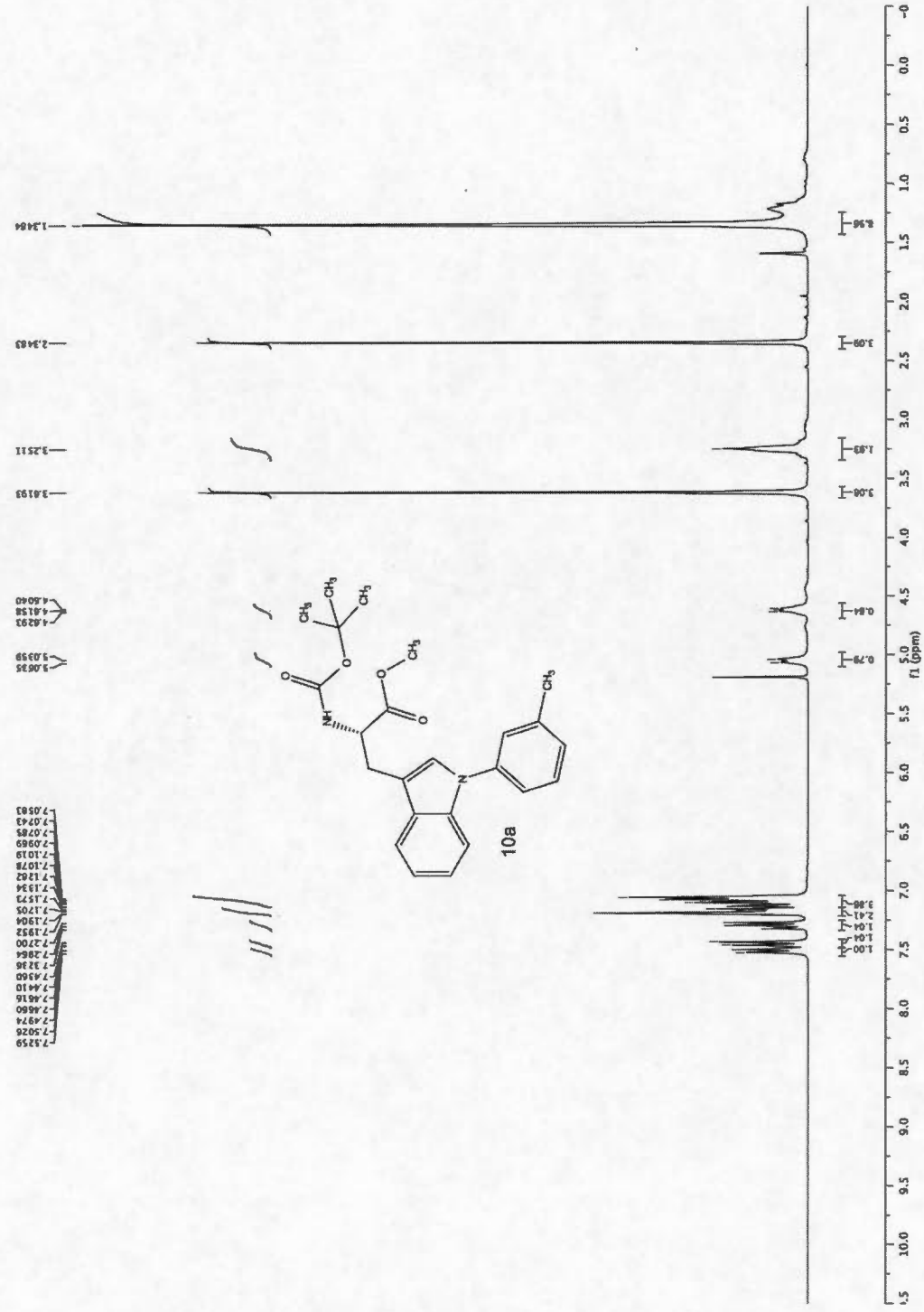
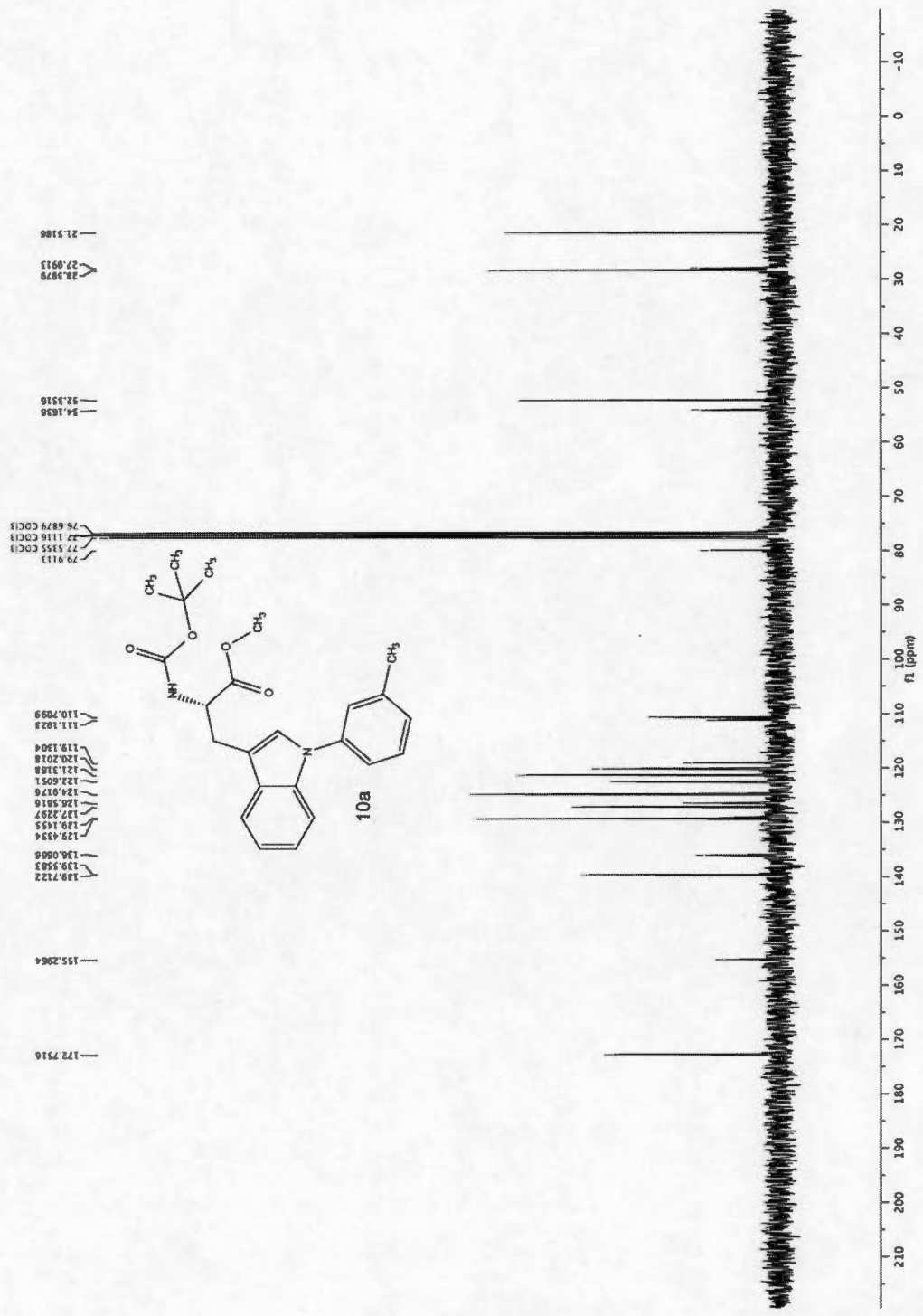
1432,07
1392,31
1278,83
1231,24
1162,99


10a
f1 (ppm)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52.3516
54.1636
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77.5355 CDCl3
79.9113
110.7099
111.1023
119.1304
120.2018
121.3168
122.6051
124.9176
126.5816
127.2297
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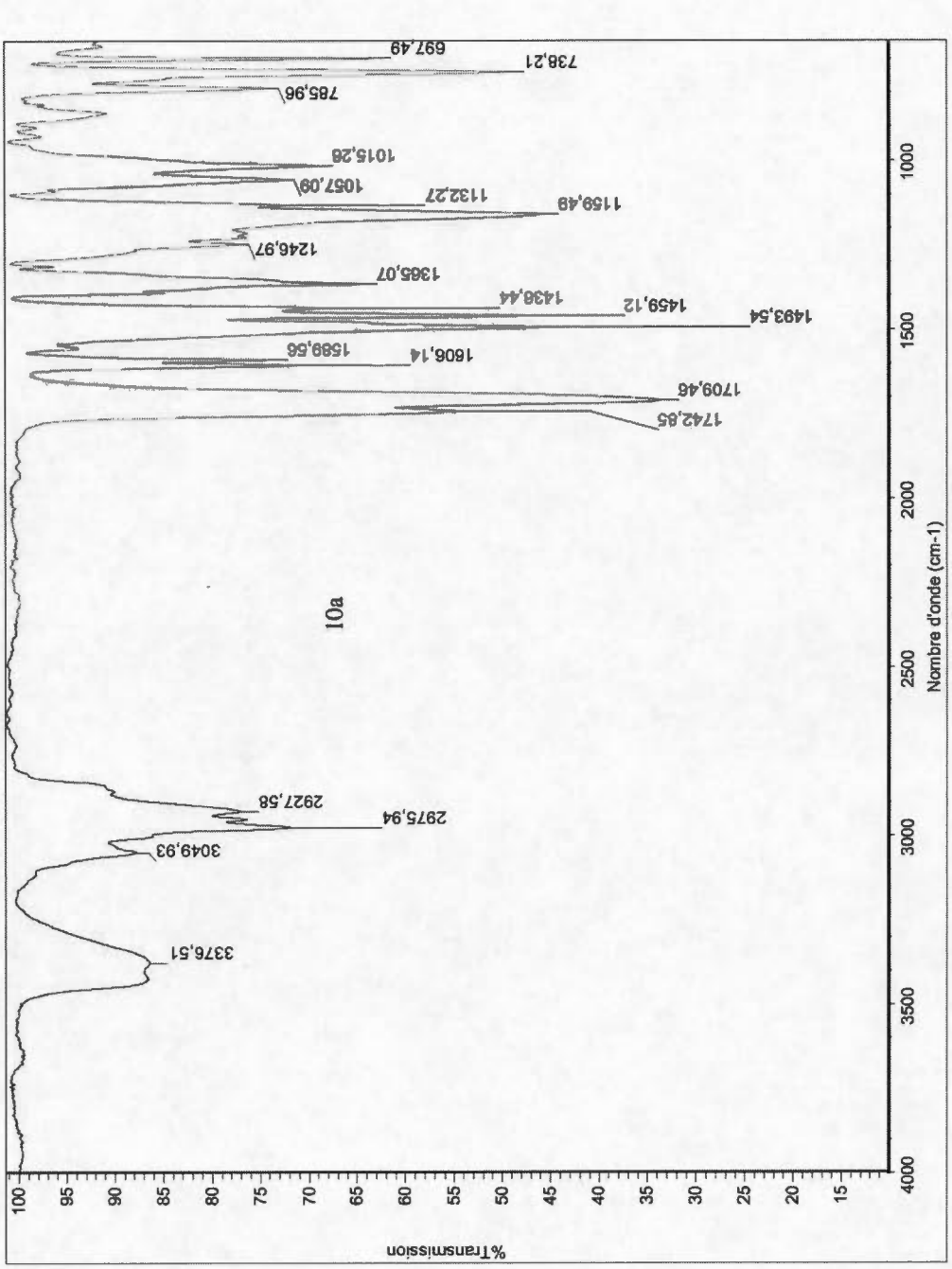
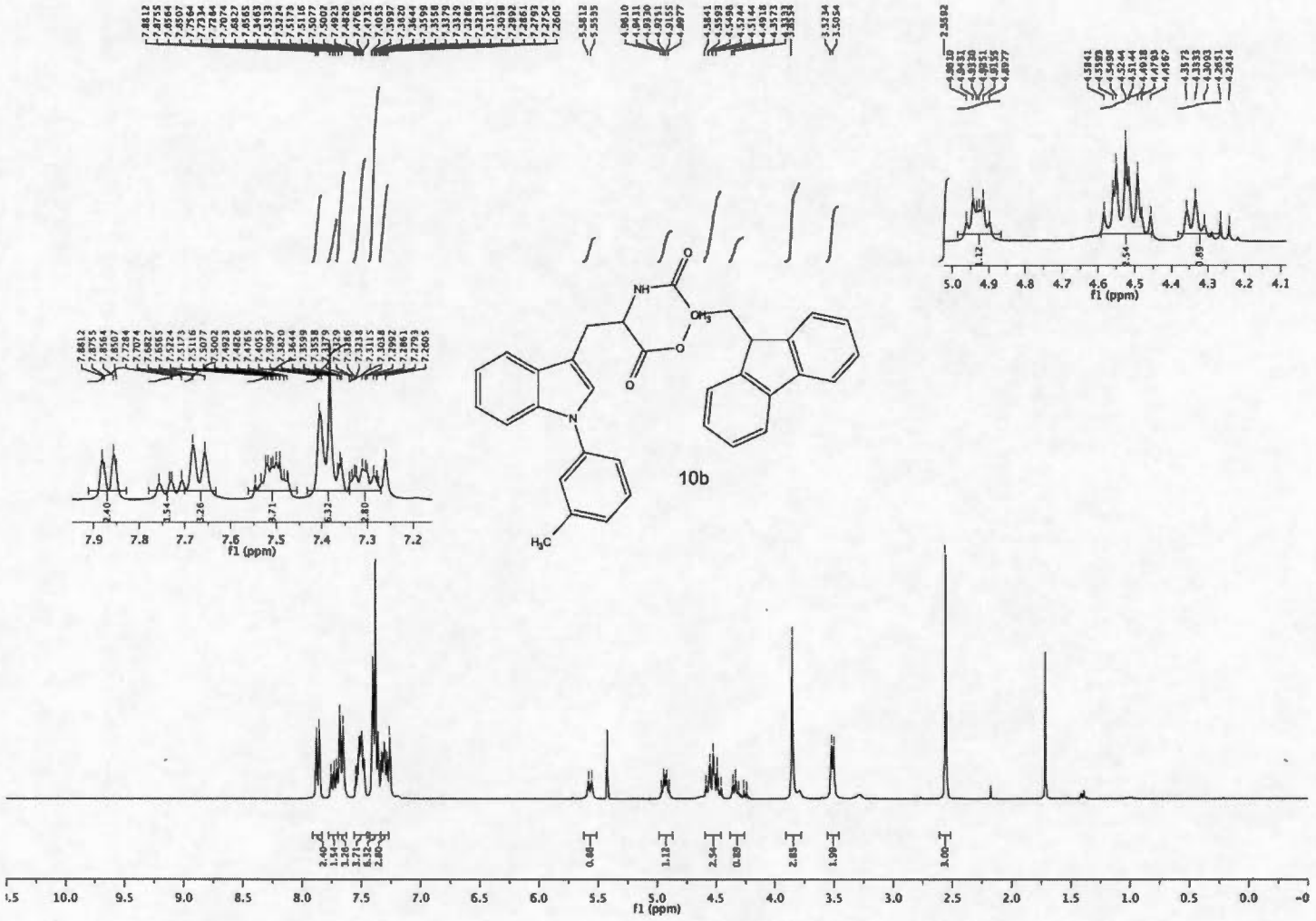
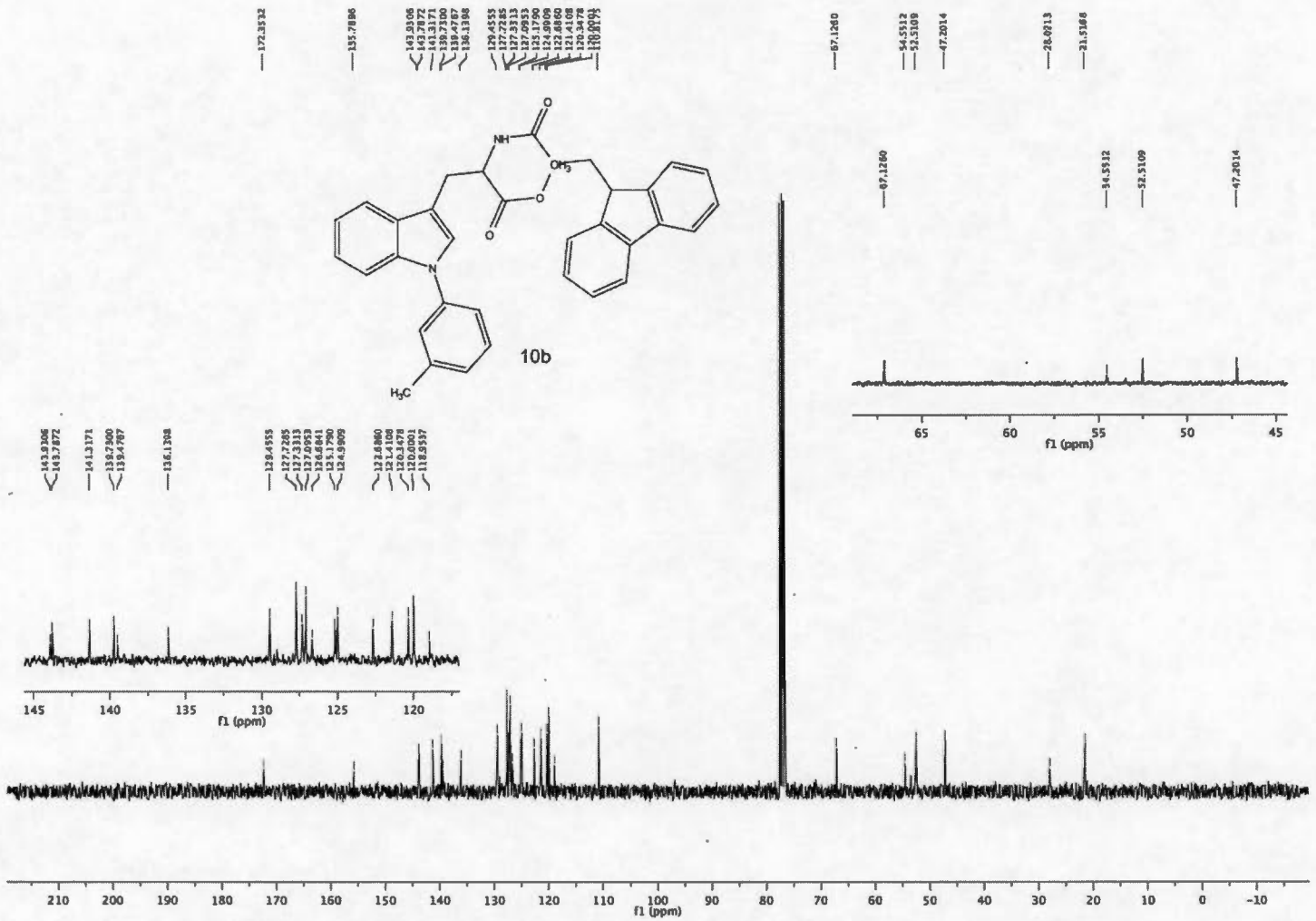
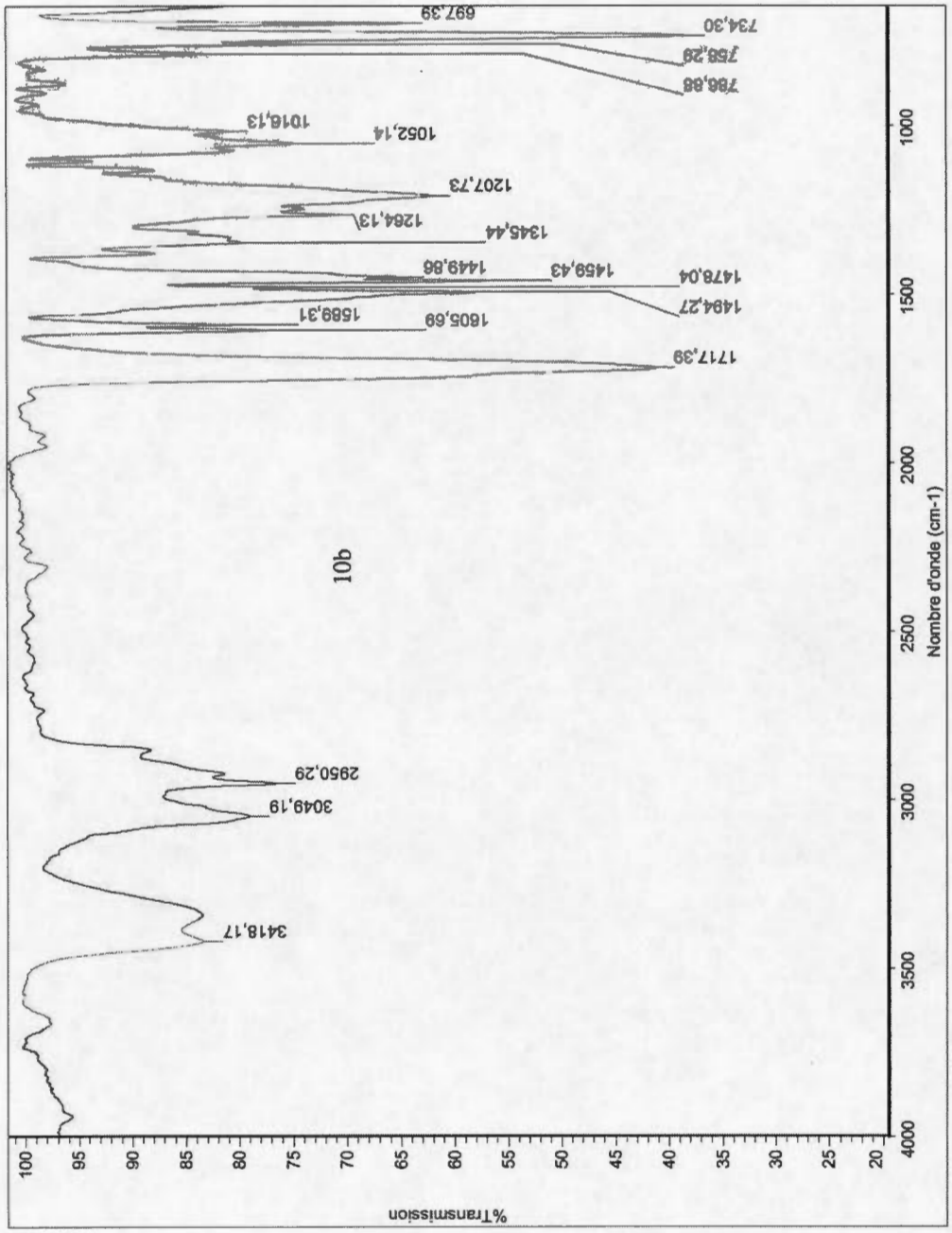
129.4334
136.0866
139.5583
139.7122
155.2964
172.7516
10a
f1 (ppm)


%Transmission
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
4000
3500
3000
2500
2000
1500
1000
Nombre d'onde (cm-1)
10a
3376,51
3049,93
2975,94
2927,58
1742,85
1709,46
1606,14
1589,56
1493,54
1459,12
1438,44
1365,07
1246,97
1159,48
1132,27
1057,09
1015,28
785,96
738,21
697,49


NH
O
O
O
OH3
N
H3C
10b
f1 (ppm)


10b
f1 (ppm)


%Transmission
Nombre d'onde (cm-1)
10b
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3049,19
2950,29
1717,39
1605,69
1589,31
1494,27
1478,04
1459,43
1449,86
1345,44
1264,13
1207,73
1052,14
1016,13
786,88
758,28
734,30
697,39

ANNEXE G

"COPPER-CATALYZED *O*-ARYLATION OF *N*-PROTECTED 1,2-AMINOALCOHOLS USING FUNCTIONALIZED TRIVALENT ORGANOBISMUTH REAGENTS" ARTICLE

Org. Biomol. Chem. **2015**, *13*, 1322

DOI : 10.1039/c4ob02497d

Titre : Copper-Catalyzed *O*-Arylation of *N*-Protected 1,2-Aminoalcohols Using Functionnalized Trivalent Organobismuth Reagents

Auteurs : Pauline Petiot, Julien Dansereau, Martin Hébert, Imène Khene, Tabinda Ahmad, Samira Samaali, Maxime Leroy, Francis Pinsonneault, Claude Legault et Alexandre Gagnon*

Organic & Biomolecular Chemistry

COMMUNICATION

Copper-catalyzed O-arylation of N-protected 1,2-aminoalcohols using functionalized trivalent organobismuth reagents†

Pauline Petiot,[a,c] Julien Dansereau,[a,c] Martin Hébert,[a,c] Imene Khene,[a,c] Tabinda Ahmad,[a,c] Samira Samaali,[a,c] Maxime Leroy,[a,c] Francis Pinsonneault,[a,c] Claude Y. Legault*[b,c] and Alexandre Gagnon*[a,c]

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The O-arylation of 1,2-aminoalcohols using functionalized triarylbismuth reagents is reported. The reaction can be performed using substoichiometric amounts of copper acetate and operates under mild conditions. Good functional group tolerance is observed, giving access to a range of β-aryloxyamines. The effect provided by the amino group in the arylation reaction is investigated.

β-Aryloxyamines are frequently found in natural products and in medicinally relevant compounds. For example, this moiety has been identified in shishididemniol A (1) and B (2), two natural products extracted from a tunicate of the family Didemnidae (Fig. 1).[1] Rosiglitazone (3), an antidiabetic drug, Ulimorelin (TZP-101, 4),[2] a ghrelin inhibitor that has advanced into phase-III clinical studies, and Mexiletine (5), an antiarrhythmic drug, also contain a β-aryloxyamine. The importance of 1,2-aryloxyamines in drug discovery can be further exemplified with compounds 6–10 which are inhibitors of various biological targets for which advanced profiling has been performed.[3–7]

β-Aryloxyamines can be accessed through S_NAr reactions between 1,2-aminoalcohols and electron poor aryl halides.[8] Alternatively, these compounds can also be prepared from the same precursors through the addition of phenols using Mitsunobu conditions[9] or *via* S_N2 reactions on the corresponding mesylates or tosylates.[10] Even though these approaches are widely spread in the pharmaceutical industry, they are not free of limitations as they require the presence of electron withdrawing groups on the aryl unit (S_NAr), necessitate the derivatization of the alcohol (S_N2) or lead to the formation of side products that can complicate the isolation of the desired product (*i.e.* phosphine oxide and urea in the Mitsunobu reaction).

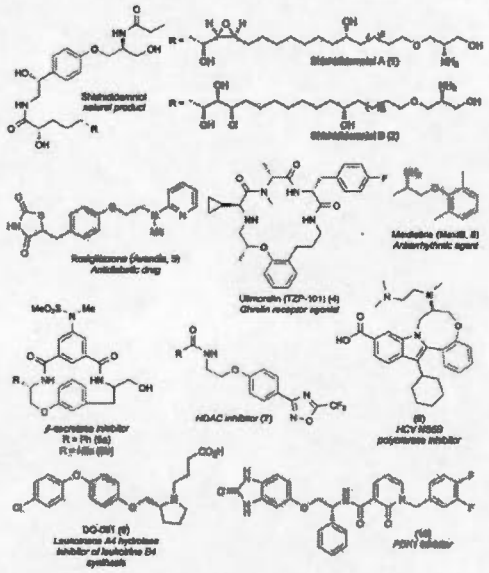

Fig. 1 Selected examples of β-aryloxyamines in natural products, drugs, and medicinal chemistry compounds.

The copper-catalyzed O-arylation of 1,2-aminoalcohols using aryl halides, as illustrated by the pioneering work of Buchwald[11] and Evano,[12] constitutes a highly efficient strategy for the preparation of β-aryloxyamines.[13–15] Surprisingly, the O-arylation of 1,2-aminoalcohols using arylmetals has been considerably less studied and to the best of our knowledge, the only example using this approach involved tetraphenylbismuth fluoride as the arylating source.[16]

We reported over the past few years a portfolio of C–C, C–N, and C–O bond forming reactions involving organobismuth reagents.[17] Organobismuthanes are an attractive class of

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[c]Centre in Green Chemistry and Catalysis

†Electronic supplementary information (ESI) available. See DOI: 10.1039/C4OB02497D

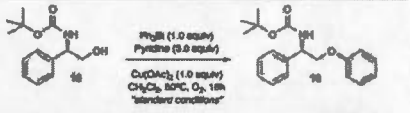
organometallic reagents that can be easily prepared from inexpensive and non-toxic bismuth salts.[18] Triarylbismuthanes are air and moisture stable and can be purified by simple silica gel chromatography. In addition, organobismuthanes show remarkable functional group tolerance, making them ideal candidates for the development of methodologies oriented towards medicinal chemistry applications.

We recently disclosed a general copper-catalyzed N-arylation reaction of azoles and diazoles using triarylbismuth reagents.[17a] In the course of our studies, we found that the arylation of the hydroxypropylindole **11** using tris-*meta*-(methylphenyl)-bismuthane proceeded exclusively on the indole to afford **12**, suggesting that an alcohol cannot be arylated under these conditions (Scheme 1). However, when the *N*-BOC-tryptophanol derivative **13** was submitted to the same conditions, the product of bis-arylation **14** was isolated in moderate yield, suggesting that the amino group activates the alcohol towards the arylation. Moreover, the yield of this reaction could be greatly improved by using 2.0 equivalents of the bismuth reagent.

David and Thieffry reported in 1983 the effect of neighbouring hydroxylic groups on the arylation reaction of alcohols using triphenylbismuth diacetate but never explored the ability of nitrogen moieties in influencing this transformation.[19] In 1986, Barton briefly studied the arylation of ethanolamine using $Ph_3Bi(OAc)_2$ and obtained a complex mixture of N-, N,N-, and N,O-arylation products.[20] These two reactions relied on pentavalent organobismuth reagents, which are usually less stable and more tedious to prepare than their trivalent counterparts. To our knowledge, the only example of O-arylation of alcohols using a trivalent bismuth reagent was reported in 1999 by Sheppard and required the use of oxone as a stoichiometric oxidizing agent.[21] We would like to report herein our study on the O-arylation of 1,2-aminoalcohols using functionalized triarylbismuthanes and our investigation into the accelerating effect provided by the amino group.

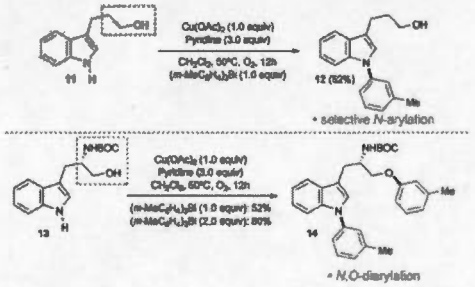
We began by optimizing the reaction conditions for the arylation of (−)-*N*-BOC-D-α-phenylglycinol **15**, a 1,2-aminoalcohol that does not possess an indolic scaffold. When this substrate was submitted to our previously identified conditions,[17a] the corresponding *O*-phenyl product **16** was isolated in 73% yield (Table 1, entry 1). Conducting the reaction under air led to a considerable reduction in the yield of the reaction, thus confirming the importance of the oxygen in this process (entry 2). To evaluate the transferability of the second aryl group from the triarylbismuthane, we next performed the reaction using 0.7 equivalent of triphenylbismuth and observed a substantial drop in the yield of **16**, demonstrating that only one aryl group can be transferred from the triarylbismuthane (entry 3). This phenomenon is well known in copper-catalyzed reactions involving organobismuth reagents[17a,b] and efforts to overcome this issue are in progress in our group. A rapid screen of different bases showed that pyridine can be replaced by triethylamine (entry 4) but not potassium carbonate (entry 5). Our studies also demonstrate that 1.2 equivalents of pyridine are sufficient to obtain an optimal yield of the arylated product (entry 6). A survey of different solvents led to the identification of toluene as the most efficient replacement for dichloromethane (entry 7). We next directed our efforts towards lowering the catalyst loading and found a moderate reduction in the yield of the arylation process upon using 0.3 equivalent of copper acetate (entry 8). In addition, reducing the reaction time to 6 hours instead of overnight provided the desired compound in similar yield (entry 9). Finally, a good yield could be obtained under catalytic conditions by conducting the reaction in toluene at 80 °C overnight (entry 10).

Table 1 Optimization of the conditions for the O-arylation of *N*-BOC-D-α-phenylglycinol **15**



Entry	Change from "standard conditions"	Yield[a] (%)
1	No change	73
2	Ambient air instead of oxygen	49
3	0.7 equiv. Ph_3Bi instead of 1.0	51
4	Et_3N instead of pyridine	73
5	K_2CO_3 instead of pyridine	31
6	1.2 equiv. pyridine instead of 3.0	67
7	Toluene instead of CH_2Cl_2	76
8[b]	0.3 equiv. $Cu(OAc)_2$ instead of 1.0	62
9[b]	0.3 equiv. $Cu(OAc)_2$ and 6 h instead of o.n.	58
10[b]	0.3 equiv. $Cu(OAc)_2$ in toluene at 80 °C	71

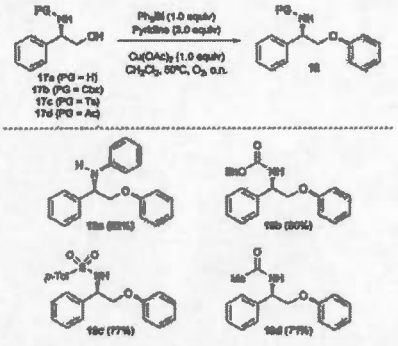
[a] Isolated yield of pure product **16**. [b] 1.2 equiv. pyridine.



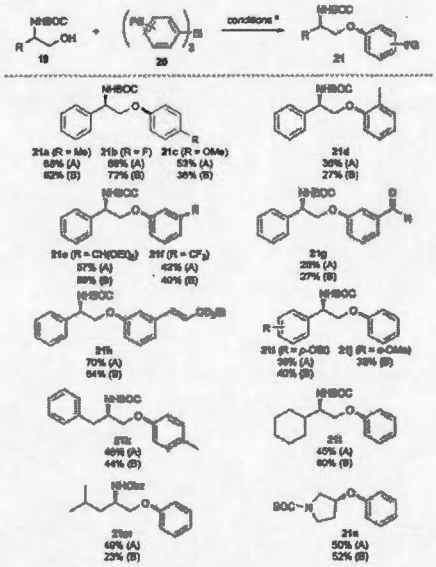
Scheme 1 N- *vs.* O-Arylation of 3-(3-hydroxypropyl)-1*H*-indole **11** and *N*-BOC-tryptophanol **13**.

The ability of other amine protecting groups in enhancing the reactivity of the alcohol towards arylation was then explored (Scheme 2). Performing the reaction directly on the unprotected phenylglycinol afforded the *N,O*-diaryl product **18a**, indicating that the amino group must imperatively be protected to prevent the undesired N-arylation pathway. A survey of different amine protecting groups demonstrated that a benzyloxycarbonyl group (**18b**) and a sulfonyl (**18c**) give slightly higher yields of the desired *O*-aryl product than an acetyl (**18d**).

The scope of the reaction was then investigated by coupling different functionalized triarylbismuthanes with various 1,2-aminoalcohols (Scheme 3). The *tert*-butyloxycarbonyl (BOC) and



Scheme 2 Impact of the protecting group on the arylation of *N*-protected phenylglycinol derivatives. PG = Protecting Group.



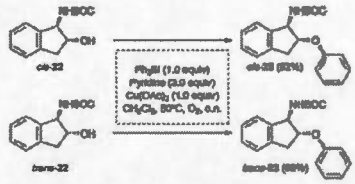
Scheme 3 O-Arylation of 1,2-aminoalcohols using functionalized organobismuthanes. [a] Conditions A: Ar_3Bi (1.0 equiv.), pyridine (1.2 equiv.), $Cu(OAc)_2$ (0.3 equiv.), toluene, 80 °C, O_2, o.n.; Conditions B: Ar_3Bi (1.0 equiv.), pyridine (3.0 equiv.), $Cu(OAc)_2$ (1.0 equiv.), CH_2Cl_2, 50 °C, O_2, o.n.

benzyloxycarbonyl (Cbz) protecting groups were selected for their ease of installation and removal. The organobismuth reagents were synthesized according to procedures that we reported previously[17a,b,d] and the protocols involving catalytic (Table 1, entry 10: conditions A) and stoichiometric (Table 1, entry 1: conditions B) amount of copper acetate were utilized. As expected, the introduction of a methyl group at the *para* position of the triarylbismuthane had little impact on the arylation process and afforded the corresponding *O*-aryl product **21a** in a reasonable yield using either conditions A or B. The transfer of an aryl group bearing an electron-withdrawing group such as a fluorine atom at the *para* position proceeded equally well, providing compound **21b** in 72% yield under conditions B. However, introducing an electron-donating group such as a methoxy at the *para* position led to a considerable drop in the efficiency of the process, as indicated by compound **21c**. The reaction also proved to be very sensitive to steric hindrance, as shown by compound **21d** where a methyl group is present at the *ortho* position of the aryl group being transferred. This phenomenon is not unprecedented and was observed previously in the context of our studies on the copper-catalyzed N-arylation of indoles[17a] and phenols.[17b] Unexpectedly, the effect of the *ortho* methyl group in the arylation reaction was found to be much higher with alcohols than with azoles and phenols. Next, we investigated the transfer of an aryl fragment possessing a diethylacetal and a trifluoromethyl group at the *meta* position and obtained the corresponding O-arylated products **21e** and **21f** in modest yields. Surprisingly, a much lower yield was observed when tris(3-formylphenyl)bismuth was utilized as the arylating agent, as indicated by compound **21g**. This is a sharp contrast to the results that we obtained with this organobismuthane in the arylation of azoles[17a] and phenols[17b] where the corresponding arylated products were obtained in excellent yields. The transfer of a phenyl group bearing an α,β-unsaturated ester at the *meta* position proved more efficient, affording compound **21h** in 70% yield under conditions A.

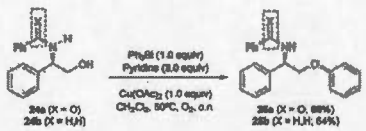
We then turned our attention to substrates where the phenyl group of phenylglycinol is substituted or replaced by an alkyl group. For instance, the *para*-ethoxy and *ortho*-methoxy derivatives **21i** and **21j** were obtained in moderate yields using this protocol. To our surprise, the insertion of a methylene unit between the phenyl group and the aminoalcohol segment led to an unexpected drop in the yield of the reaction (**21a** → **21k**). Interestingly, products **21l** and **21m** where the phenyl group is replaced by a cyclohexyl or an *iso*-butyl moiety were successfully prepared using this method. Lastly, the arylation could also be performed on a secondary alcohol, as demonstrated by compound **21n**.

In order to understand the role of the amino group in the arylation process, we performed a series of control experiments where specific geometric and functional modifications are introduced in the substrate. We first hypothesized that the NHBOC function could be promoting the O-arylation reaction through complexation of the copper species *via* the carbonyl moiety of the carbamate. To test this hypothesis, we compared the reactivity of the *cis*- and *trans*-*N*-BOC-indanol derivatives *cis*-**22** and *trans*-**22** using conditions B (Scheme 4). In the event, a higher yield was observed for the *trans* stereoisomer, suggesting that the accelerating effect provided by the amino group is not a result of a complexation of metallic intermediates by the carbonyl group.

To further investigate the hypothesis that the C=O bond of the carbamate could be directing the reaction through com-



Scheme 4 Study of the effect of the conformational effect in the O-arylation of *N*-BOC-1-amino-2-indanol 22.



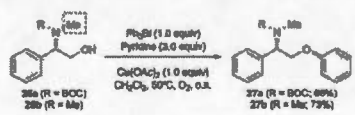
Scheme 5 Comparison of *N*-benzoyl 24a and *N*-benzyl 24b protecting groups in the copper-catalyzed arylation of N-protected phenylglycinol.

plexation of the copper species, we compared the reactivity of the *N*-benzoyl and *N*-benzyl derivatives 24a and 24b of phenylglycinol in the arylation reaction (Scheme 5). Should there be a complexation involved, it would be reasonable to expect a much greater yield with the benzoyl compound 24a than with the benzyl analogue 24b. To our surprise, similar yields of the *O*-aryl products were obtained with both derivatives, thus invalidating our complexation hypothesis.

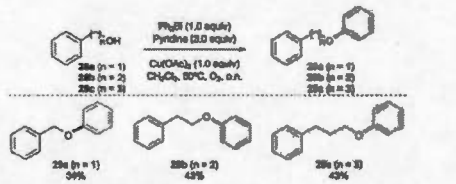
We then hypothesized that the amide N–H bond could be responsible for the acceleration of the arylation reaction through formation of copper species where the amide acts as a ligand. To test this hypothesis, we performed the arylation reaction using the *N*-methyl derivatives 26a and 26b and observed a good conversion to the corresponding *O*-aryl products 27a,b, thus discrediting this second hypothesis (Scheme 6).

In order to better evaluate the importance of the amino group in the reaction, we then performed the arylation on phenethylalcohol 28b, a simple alcohol with no amino group and observed a 30% drop in the yield of the reaction compared to phenylglycinol 15 (Scheme 7). This result clearly indicates that the β-amino group has a dramatic effect on the arylation process. The arylation of benzyl alcohol 28a and 3-phenyl-1-propanol 28c provided the corresponding *O*-phenyl ethers 29a and 29c in similar yields as 28b.

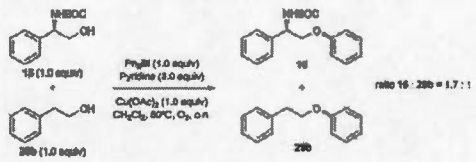
To evaluate the difference in reactivity between simple alcohols and 1,2-aminoalcohols more accurately, we next performed a competition experiment between *N*-BOC-



Scheme 6 Arylation of *N*-BOC-*N*-methyl and *N*,*N*-dimethyl phenylglycinol derivatives 26a and 26b.



Scheme 7 O-Arylation of benzyl alcohol 28a, phenethyl alcohol 28b, and 3-phenyl-1-propanol 28c.

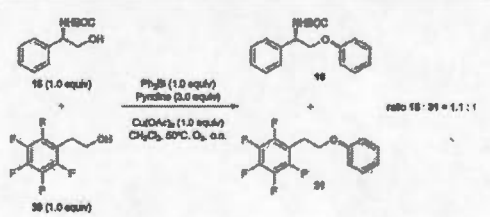


Scheme 8 Competition studies between phenethylalcohol 28b and *N*-BOC-phenylglycinol 15.

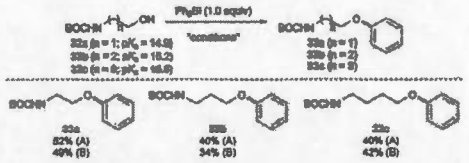
phenylglycinol 15 and phenethylalcohol 28b (Scheme 8). After 16 hours, the ^{1}H-NMR analysis of the crude mixture indicated a ratio of *O*-phenyl-*N*-BOC phenylglycinol 16 over 29b of 1.7 : 1.0, suggesting that an aminoalcohol is more reactive than a simple alcohol.

We then postulated that the difference in reactivity between 1,2-aminoalcohols and simple alcohols could derive from an inductive effect generated by the β-amino group, effectively lowering the pK_a of the alcohol moiety. To test this hypothesis, we performed a second competition experiment between *N*-BOC-phenylglycinol 15 and pentafluorophenethylalcohol 30 (Scheme 9). After 16 hours, the ^{1}H-NMR analysis of the crude mixture showed a ratio of the *O*-phenyl-*N*-BOC phenylglycinol 16 over *O*-phenylpentafluorophenethylether 31 of 1.1 : 1.0, thus demonstrating that the pentafluoroalcohol 30 has a similar reactivity than *N*-BOC-phenylglycinol 15 and therefore suggesting that the presence of electron-withdrawing groups increases the reactivity of an alcohol.

To furnish further evidence of this effect, the aqueous pK_a values for alcohols 15, 28b, and 30 were calculated using a recent method reported by Pulay *et al.*[22] The calculations were carried out using ORCA 3.0.1.[25] These values were calculated to be 15.8



Scheme 9 Competition studies between 2-(pentafluorophenyl)ethanol 30 and *N*-BOC-phenylglycinol 15.



Scheme 10 O-Arylation of *N*-BOC-ethanolamine **32a**, 3-(*N*-BOC-amino)-1-propanol **32b**, and 4-(*N*-BOC-amino)-1-butanol **32c**. Conditions A: Ar_3Bi (1.0 equiv.), pyridine (1.2 equiv.), $Cu(OAc)_2$ (0.3 equiv.), toluene, 80 °C, O_2, o.n.; Conditions B: Ar_3Bi (1.0 equiv.), pyridine (3.0 equiv.), $Cu(OAc)_2$ (1.0 equiv.), CH_2Cl_2, 50 °C, O_2, o.n.

for **15**, 17.3 for **28b**, and 15.6 for **30**. These values are in line with the relative reactivities illustrated in Schemes 8 and 9, thus supporting the inductive effect hypothesis.

To further support our hypothesis, we performed the O-arylation of aminoalcohols **32a–c** where the distance between the amino group and the alcohol is systematically increased by one methylene unit (Scheme 10). The results indicate that the yield is higher for *N*-BOC-ethanolamine **32a** which has the lowest pK_a. The yield then decreases as the pK_a increases, as shown by products **33b** and **33c**.

The results from Schemes 7–10 support our hypothesis that an amino group in β-position relative to an alcohol accelerates the O-arylation reaction mainly *via* an inductive effect.

Conclusions

In summary, we have developed a copper-catalyzed O-arylation reaction of 1,2-aminoalcohols using functionalized triarylbismuthanes. The reaction is promoted by catalytic amounts of copper acetate and tolerates a variety of substituents on the organobismuthane, giving access to functionalized β-aryloxyamines. Different protecting groups can be used on the aminoalcohol, such as BOC, Cbz, Ac, and Ts. Finally, we demonstrated that the presence of an amino group in β relative to the alcohol provides an increase in reactivity, probably through inductive effect. The application of this protocol to the arylation of other hydroxy-containing substrates is in progress in our group and results will be reported in due course.

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ANNEXE H

"COPPER-CATALYZED *O*-ARYLATION OF *N*-PROTECTED 1,2-AMINOALCOHOLS USING FUNCTIONALIZED TRIVALENT ORGANOBISMUTH REAGENTS" SUPPORTING INFORMATION

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Titre : Copper-Catalyzed *O*-Arylation of *N*-Protected 1,2-Aminoalcohols Using Functionnalized Trivalent Organobismuth Reagents

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P. Petiot, J. Dansereau, M. Hébert, I. Khene, T. Ahmad, S. Samaali, M. Leroy, F. Pinsonneault, C. Y. Legault and A. Gagnon

Supporting Information

Copper-Catalyzed *O*-Arylation of *N*-Protected 1,2-Aminoalcohols Using Functionalized Trivalent Organobismuth Reagents

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Table of content:

P. Petiot, J. Dansereau, M. Hébert, I. Khene, T. Ahmad, S. Samaali, M. Leroy, F. Pinsonneault, C. Y. Legault and A. Gagnon

1. General information

Unless otherwise indicated, all reactions were run under argon in non-flame dried glassware. For reactions performed under oxygen, 99.6% extra dry oxygen was used. Unless otherwise stated, commercial reagents were used without further purification. Grignard reagents were prepared by conventional methods using metallic magnesium or via Knochel's procedure.[1] Triphenylbismuth and anhydrous bismuth chloride 99.999% were purchased from Strem Chemicals. Triarylbismuthanes were prepared according to procedures that we previously reported.[2,3,4] Anhydrous solvents were obtained using a MBRAUN (model MB-SPS 800) encapsulated solvent purification system. The evolution of reactions was monitored by analytical thin-layer chromatography using silica gel 60 F254 precoated plates. Flash chromatography was performed employing 230-400 mesh silica (Silicycle) using the indicated solvent system according to standard techniques.[5] Melting points were taken on an Electrothermal Mel-TEMP and are uncorrected. Nuclear magnetic resonance spectra (^{1}H, ^{13}C) were recorded on a Bruker Avance-III 300MHz spectrometer. Chemical shifts for ^{1}H-NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, s(br) = broad singlet, d = doublet, t = triplet, q = quartet, qt = quintuplet, dd = doublet of doublet, m = multiplet), coupling constant J in Hz and integration. Chemical shifts for ^{13}C spectra are recorded in parts per million from tetramethylsilane using the central peak of deuterochloroform (δ 77.16 ppm) as the internal standard. IR spectra were recorded on a Thermo Scientific Nicolet 6700 PT-IR from thin films and are reported in reciprocal centimeters (cm^{-1}). HRMS were performed at Université du Québec à Montréal (nanoQAM center) on Agilent Technologies, LC 1200 Series / 6210 TOF LCMS analyzer using the electrospray (ESI) mode.

P. Petiot, J. Dansereau, M. Hébert, I. Khene, T. Ahmad, S. Samaali, M. Leroy, F. Pinsonneault, C. Y. Legault and A. Gagnon

2. Triarylbismuthanes used in the *O*-arylation of *N*-protected 1,2-aminoalcohols

The organobismuthanes used in this publication are illustrated in **Figure S1**.

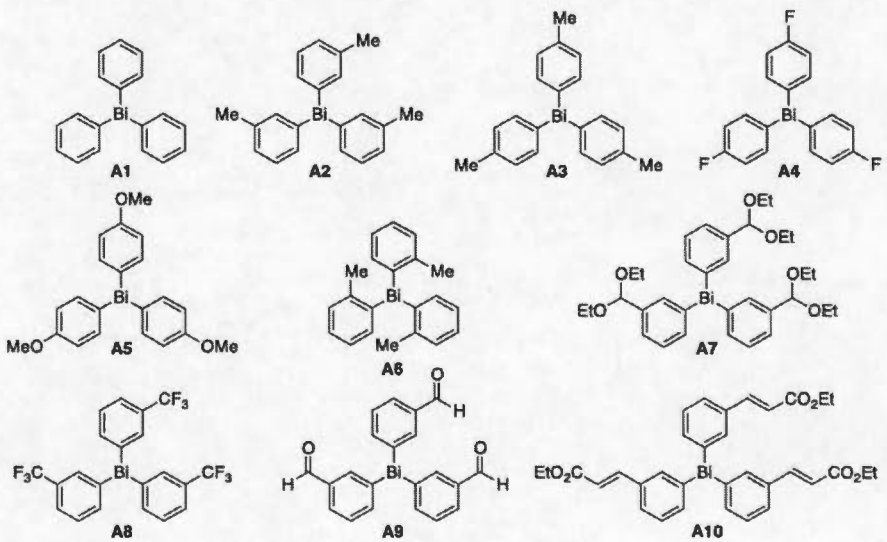


Figure S1. Functionalized organobismuthanes used in this publication. Triphenylbismuth was purchased from Strem. Organobismuthanes **A3**, **A4**, **A6**, **A7**, **A9** were synthesized according to: P. Petiot and A. Gagnon, *Eur. J. Org. Chem.*, **2013**, 5282. Organobismuthanes **A2**, **A5**, **A8**, **A10** were synthesized according to: P. Petiot, J. Dansereau and A. Gagnon, *RSC Adv.*, **2014**, 22255.

P. Petiot, J. Dansereau, M. Hébert, I. Khene, T. Ahmad, S. Samaali, M. Leroy, F. Pinsonneault, C. Y. Legault and A. Gagnon

3. General procedures for the *O*-arylation of aminoalcohols

Compounds **14**, **16**, **18a-d**, **21a-n**, ***cis*-23**, ***trans*-23**, **25a,b**, **27a,b**, **29a-c** and **33a-c** were prepared according to the following procedures:

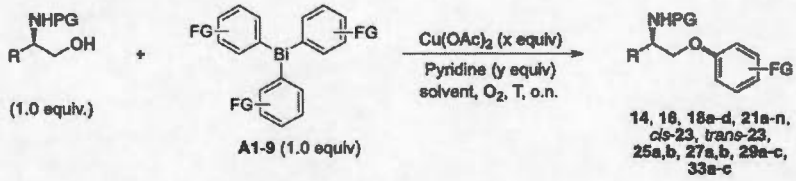


Table S1. Reaction conditions: Method A and B.

Method	Amino-alcohol (n equiv)	Ar_3Bi (A) (m equiv)	$Cu(OAc)_2$ (x equiv)	Pyridine (y equiv)	Solvent	Temperature
A	1.0	1.0	0.3	1.2	toluene	80°C
B	1.0	1.0	1.0	3.0	dichloromethane	50°C

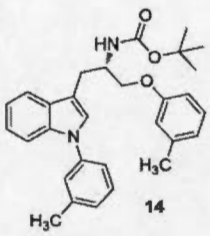
Method A: In a sealed tube, triarylbismuthine **A** (1.0 equiv) was added, followed by copper (II) acetate (0.3 equiv) and the aminoalcohol (1.0 equiv). The reagents were dissolved in anhydrous toluene (4 mL) and pyridine (1.2 equiv) was added to the mixture. The reaction tube was purged with dry oxygen for 30 seconds, sealed and heated at 80°C overnight. The reaction mixture was cooled to r.t., transferred and rinsed with EtOAc in a round bottom flask. Silica gel was added and the mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using the indicated eluent system to give the corresponding product.

Method B: Idem as method **A** except for copper (II) acetate (1.0 equiv instead of 0.3 equiv), pyridine (3.0 equiv instead of 1.2 equiv), in dichloromethane at 50°C.

P. Petiot, J. Dansereau, M. Hébert, I. Khene, T. Ahmad, S. Samaali, M. Leroy, F. Pinsonneault, C. Y. Legault and A. Gagnon

4. Characterization of products

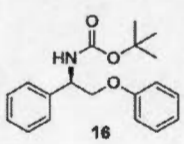
(*S*)-*tert*-Butyl-(1-(1-(*m*-tolyl)-1*H*-indol-3-yl)-3-(*m*-tolyloxy)propan-2-yl)carbamate (14)



14

Method B was followed on a 0.17 mmol scale starting from *N*-BOC-tryptophanol **13** and **A2**. The crude product was purified on silica gel (10% EtOAc/hexanes) to afford **14** as a yellow oil (42 mg, 53%): R_f 0.65 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.64 (d, J = 7.7 Hz, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.26 (t, J = 7.7 Hz, 1H), 7.14-7.02 (m, 7H), 6.71-6.62 (m, 3H), 4.98 (d, J = 7.8 Hz, 1H), 4.24 (s(br), 1H), 3.86 (qd, J = 9.2, 3.3 Hz, 2H), 3.13-3.10 (m, 2H), 2.32 (s, 3H), 2.23 (s, 3H), 1.38 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.9, 155.6, 139.7, 136.1, 129.4, 129.3, 127.0, 126.9, 124.8, 122.6, 122.0, 121.2, 120.2, 119.5, 115.6, 113.0, 111.6, 110.7, 68.1, 50.6, 28.6, 27.3, 21.6, 21.5; IR (neat) 3403, 3048, 2978, 2921, 2860, 1712, 1693, 1605, 1493, 1160; HRMS (ESI) calcd for $C_{30}H_{34}N_2O_3$: 470.2569, found 493.2457 (M+Na).

(*R*)-*tert*-Butyl-(2-phenoxy-1-phenylethyl)carbamate (16)

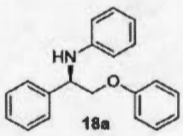


16

Method B was followed on a 0.21 mmol scale starting from *(R)-tert*-butyl (2-hydroxy-1-phenylethyl)carbamate **15** and **A1**. The crude product was purified on silica gel (10% EtOAc/hexanes) to afford **16** as a yellow solid (48 mg, 73%): m.p. 82°C. Spectral data was identical to literature[6]: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34-7.26 (m, 4H), 7.23-7.18 (m, 3H), 6.89 (t, J = 7.3 Hz, 1H), 6.82 (d, J = 8.1 Hz, 2H), 5.26 (s(br), 1H), 4.99 (s(br), 1H), 4.19-4.08 (m, 2H), 1.36 (s, 9H).

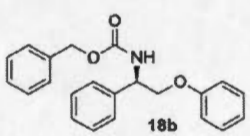
P. Petiot, J. Dansereau, M. Hébert, I. Khene, T. Ahmad, S. Samaali, M. Leroy, F. Pinsonneault, C. Y. Legault and A. Gagnon

(*R*)-*N*-(2-Phenoxy-1-phenylethyl)aniline (18a)



Method B was followed on a 0.36 mmol scale starting from *(R)*-2-phenyl-2-(phenylamino)ethanol **17a** and **A1**. The crude product was purified on silica gel (5% EtOAc/hexanes) to afford **18a** as a white solid (65 mg, 62%): m.p. 124°C; R_f 0.66 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.52-7.49 (m, 2H), 7.41-7.27 (m, 5H), 7.15-7.09 (m, 2H), 7.05-6.96 (m, 1H), 6.94-6.91 (m, 2H), 6.71 (t, J = 7.4 Hz, 1H), 6.60-6.57 (m, 2H), 4.74 (dd, J = 8.3, 3.8 Hz, 1H), 4.65 (s(br), 1H), 4.24 (dd, J = 9.6, 3.9 Hz, 1H), 4.08 (dd, J = 9.6, 8.5 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.4, 147.5, 140.2, 129.6, 129.2, 128.9, 127.8, 127.0, 121.4, 118.0, 114.8, 114.1, 72.0, 58.2; IR (neat) 3405, 3056, 3026, 2922, 2850, 1598, 1496, 1453, 1234, 1173, 748, 690; HRMS (ESI) calcd for $C_{20}H_{19}NO$: 289.1467, found 290.1548 (M+H). To further confirm the chemoselectivity of the reaction and the structure of the compound, we compared the data with the *N,N*-diphenyl isomer from the literature and found the two compounds to be different.[7]

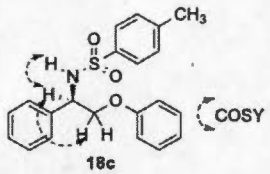
(*R*)-Benzyl (2-phenoxy-1-phenylethyl)carbamate (18b)



Method B was followed on a 0.18 mmol scale starting from *(R)*-benzyl (2-hydroxy-1-phenylethyl)carbamate **17b** and **A1**. The crude product was purified on silica gel (5% EtOAc/hexanes) to afford **18b** as a white solid (50 mg, 80%): m.p. 84°C; R_f 0.40 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.38-7.21 (m, 12H), 6.92 (t, J = 7.3 Hz, 1H), 6.83 (d, J = 7.9 Hz, 2H), 5.59 (s(br), 1H), 5.13-5.03 (m, 3H), 4.24-4.14 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.3, 156.0, 139.5, 136.4, 129.6, 128.7, 128.6, 128.3, 127.9, 126.9, 121.4, 114.7, 70.4, 67.1, 54.5; IR (neat) 3403, 3324, 3063, 3032, 2937, 1698, 1599, 1496, 1456, 1239, 1050, 753, 696; HRMS (ESI) calcd for $C_{22}H_{21}NO_3$: 347.1521, found 348.1595 (M+H).

P. Petiot, J. Dansereau, M. Hébert, I. Khene, T. Ahmad, S. Samaali, M. Leroy, F. Pinsonneault, C. Y. Legault and A. Gagnon

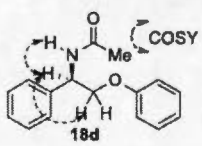
(*R*)-4-Methyl-*N*-(2-phenoxy-1-phenylethyl)benzenesulfonamide (18c)



18c

Method B was followed on a 0.17 mmol scale starting from *(R)*-*N*-(2-hydroxy-1-phenylethyl)-4-methyl-*S*-methylenebenzenesulfinamide **17c** and **A1**. The crude product was purified on silica gel (10% EtOAc/hexanes) to afford **18c** as a colorless oil (48 mg, 77%): R_f 0.31 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.65 (d, J = 8.3 Hz, 2H), 7.31-7.26 (m, 7H), 7.20 (d, J = 8.0 Hz, 2H), 7.00 (t, J = 7.4 Hz, 1H), 6.81-6.79 (m, 2H), 5.37 (d, J = 5.5 Hz, 1H), 4.72 (q, J = 5.3 Hz, 1H), 4.18-4.06 (m, 2H), 2.42 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 157.8, 143.3, 137.4, 137.2, 129.5, 129.4, 128.6, 128.1, 127.3, 121.5, 114.5, 70.4, 57.1, 21.5; IR (neat) 3305, 3075, 3050, 2983, 2925, 1740, 1373, 1235, 1044, 754, 691; HRMS (ESI) calcd for $C_{21}H_{21}NO_3S$: 367.1242, found 390.1139 (M+Na). The connectivity was further confirmed by COSY-NMR analysis, demonstrating that the *O*-phenyl isomer has been formed.

(*R*)-*N*-(2-Phenoxy-1-phenylethyl)acetamide (18d)

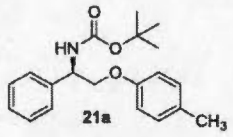


18d

Method B was followed on a 0.28 mmol scale starting from *(R)*-*N*-(2-hydroxy-1-phenylethyl)acetamide **17d** and **A1**. The crude product was purified on silica gel (15% EtOAc/hexanes) to afford **18d** as a yellow oil (51 mg, 71%): R_f 0.10 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.48-7.41 (m, 3H), 7.39-7.31 (m, 4H), 7.03 (t, J = 7.4 Hz, 1H), 6.97-6.94 (m, 2H), 6.45 (d, J = 7.6 Hz, 1H), 5.49-5.43 (m, 1H), 4.35-4.26 (m, 2H), 2.10 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.7, 158.4, 139.3, 129.6, 128.7, 127.8, 127.1, 121.4, 114.7, 69.9, 52.5, 23.4; IR (neat) 3438, 3285, 3061, 3028, 2920, 2859, 1650, 1599, 1494, 1453, 1238, 751, 690; HRMS (ESI) calcd for $C_{16}H_{17}NO_2$: 255.1259, found 256.1310 (M+H). The connectivity was further confirmed by COSY-NMR analysis, demonstrating that the *O*-phenyl isomer has been formed.

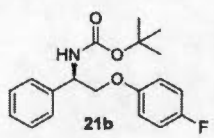
P. Petiot, J. Dansereau, M. Hébert, I. Khene, T. Ahmad, S. Samaali, M. Leroy, F. Pinsonneault, C. Y. Legault and A. Gagnon

(*R*)-*tert*-Butyl (1-phenyl-2-(*p*-tolyloxy)ethyl)carbamate (21a)



Method A was followed on a 0.21 mmol scale starting from *(R)-tert*-butyl (2-hydroxy-1-phenylethyl)carbamate **15** and **A3**. The crude product was purified on silica gel (5% EtOAc/hexanes) to afford **21a** as a colorless oil (47 mg, 68%): R_f 0.55 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.41-7.26 (m, 5H), 7.07 (d, J = 8.3 Hz, 2H), 6.78 (d, J = 8.6 Hz, 2H), 5.34 (s(br), 1H), 5.05 (s(br), 1H), 4.24-4.12 (m, 2H), 2.29 (s, 3H), 1.44 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 156.3, 155.4, 140.0, 130.5, 130.0, 128.6, 127.6, 126.8, 114.6, 79.8, 70.8, 28.4, 20.5; IR (neat) 3463, 3339, 3081, 3031, 2976, 2926, 2869, 1697, 1509, 1365, 1236, 1164, 1047, 699; HRMS (ESI) calcd for $C_{20}H_{25}NO_3$: 327.1834, found 350.1717 (M+Na).

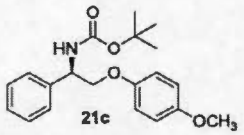
(*R*)-*tert*-Butyl (2-(4-fluorophenoxy)-1-phenylethyl)carbamate (21b)



Method B was followed on a 0.21 mmol scale starting from *(R)-tert*-butyl (2-hydroxy-1-phenylethyl)carbamate **15** and **A4**. The crude product was purified on silica gel (5% EtOAc/hexanes) to afford **21b** as a yellow solid (50 mg, 72%): m.p. 86°C; R_f 0.57 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.39-7.26 (m, 5H), 6.98-6.91 (m, 2H), 6.84-6.79 (m, 2H), 5.28 (s(br), 1H), 5.04 (s(br), 1H), 4.22-4.12 (m, 2H), 1.43 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 159.1, 156.0, 155.3, 154.6, 139.7, 128.6, 127.7, 126.8, 116.0, 115.8, 115.7, 79.9, 71.3, 28.4; IR (neat) 3445, 3018, 2979, 2931, 1704, 1506, 1367, 1215, 1165, 907, 751, 731; HRMS (ESI) calcd for $C_{19}H_{22}FNO_3$: 331.1584, found 354.1476 (M+Na).

P. Petiot, J. Dansereau, M. Hébert, I. Khene, T. Ahmad, S. Samaali, M. Leroy, F. Pinsonneault, C. Y. Legault and A. Gagnon

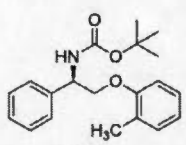
(*R*)-*tert*-Butyl (2-(4-methoxyphenoxy)-1-phenylethyl)carbamate (21c)



21c

Method A was followed on a 0.21 mmol scale starting from *(R)-tert*-butyl (2-hydroxy-1-phenylethyl)carbamate **15** and **A5**. The crude product was purified on silica gel (10% EtOAc/hexanes) to afford **21c** as a yellow oil (38 mg, 53%): R_f 0.43 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.26 (m, 5H), 6.82 (s, 4H), 5.33 (s(br), 1H), 5.02 (s(br), 1H), 4.21-4.10 (m, 2H), 3.76 (s, 3H), 1.43 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 155.4, 154.2, 152.6, 128.6, 127.6, 126.8, 115.7, 114.7, 79.8, 71.5, 64.9, 55.8, 28.4; IR (neat) 3456, 3345, 3100, 3063, 2975, 2932, 2834, 1701, 1505, 1461, 1227, 1162, 1032, 699; HRMS (ESI) calcd for $C_{20}H_{25}NO_4$: 343.1784, found 366.1665 (M+Na).

(*R*)-*tert*-Butyl (1-phenyl-2-(*o*-tolyloxy)ethyl)carbamate (21d)

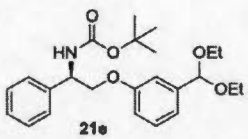


21d

Method A was followed on a 0.21 mmol scale starting from *(R)-tert*-butyl (2-hydroxy-1-phenylethyl)carbamate **15** and **A6**. The crude product was purified on silica gel (5% EtOAc/hexanes) to afford **21d** as a yellow solid (25 mg, 36%): m.p. 100°C; R_f 0.54 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.41-7.26 (m, 5H), 7.15-7.10 (m, 2H), 6.86 (t, J = 7.1 Hz, 1H), 6.77 (d, J = 8.3 Hz, 1H), 5.31 (s(br), 1H), 5.11 (s(br), 1H), 4.24 (dd, J = 9.3, 4.5 Hz, 1H), 4.16-4.11 (m, 1H), 2.17 (s, 3H), 1.44 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 156.4, 155.4, 139.8, 130.8, 128.5, 127.6, 126.9, 126.8, 120.9, 111.0, 79.8, 70.8, 29.7, 28.4, 16.3; IR (neat) 3341, 3063, 3031, 2976, 2926, 2853, 1703, 1495, 1243, 1169, 750; HRMS (ESI) calcd for $C_{20}H_{25}NO_3$: 327.1834, found 350.1717 (M+Na).

P. Petiot, J. Dansereau, M. Hébert, I. Khene, T. Ahmad, S. Samaali, M. Leroy, F. Pinsonneault, C. Y. Legault and A. Gagnon

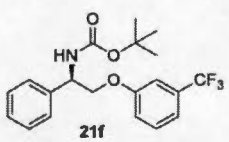
(*R*)-*tert*-Butyl (2-(3-(diethoxymethyl)phenoxy)-1-phenylethyl)carbamate (21e)



21e

Method A was followed on a 0.21 mmol scale starting from *(R)-tert*-butyl (2-hydroxy-1-phenylethyl)carbamate **15** and **A7**. The crude product was purified on silica gel (10% EtOAc/hexanes) to afford **21e** as a colorless oil (50 mg, 57%): R_f 0.29 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.44-7.39 (m, 4H), 7.36-7.29 (m, 2H), 7.10-7.05 (m, 2H), 6.86 (dd, J = 7.8, 2.0 Hz, 1H), 5.48 (s, 1H), 5.38 (s, 1H), 5.09 (s(br), 1H), 4.30-4.19 (m, 2H), 3.70-3.51 (m, 4H), 1.47 (s, 9H), 1.26 (t, J = 7.1 Hz, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.5, 155.4, 140.9, 129.3, 128.6, 127.6, 126.8, 119.6, 114.6, 112.7, 101.3, 79.8, 70.6, 61.1, 31.6, 28.4, 22.7, 15.2, 14.1, 11.5; IR (neat) 3344, 3078, 3065, 2976, 2931, 2729, 1692, 1597, 1259, 1166, 1050; HRMS (ESI) calcd for $C_{24}H_{33}NO_5$: 415.2359, found 438.2245 (M+Na).

(*R*)-*tert*-Butyl (1-phenyl-2-(3-(trifluoromethyl)phenoxy)ethyl)carbamate (21f)

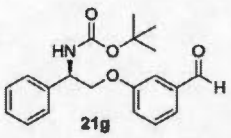


21f

Method A was followed on a 0.21 mmol scale starting from *(R)-tert*-butyl (2-hydroxy-1-phenylethyl)carbamate **15** and **A8**. The crude product was purified on silica gel (10% EtOAc/hexanes) to afford **21f** as a yellow oil (34 mg, 42%): R_f 0.54 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.30 (m, 6H), 7.21 (d, J = 7.7 Hz, 1H), 7.10-7.04 (m, 2H), 5.25 (s(br), 1H), 5.08 (s(br), 1H), 4.30-4.21 (m, 2H), 1.44 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.5, 155.3, 139.4, 132.5, 132.1, 131.7, 131.3, 130.0, 128.7, 127.8, 126.8, 125.7, 122.1, 118.0, 111.6, 80.0, 70.9, 28.3; IR (neat) 3473, 3329, 3079, 3033, 2978, 2931, 1703, 1493, 1452, 1238, 1167, 1126, 698; HRMS (ESI) calcd for $C_{20}H_{22}F_3NO_3$: 381.1552, found 404.1446 (M+Na).

P. Petiot, J. Dansereau, M. Hébert, I. Khene, T. Ahmad, S. Samaali, M. Leroy, F. Pinsonneault, C. Y. Legault and A. Gagnon

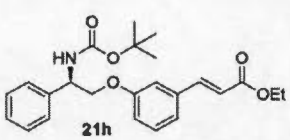
(*R*)-*tert*-Butyl (2-(3-formylphenoxy)-1-phenylethyl)carbamate (21g)



21g

Method B was followed on a 0.21 mmol scale starting from *(R)-tert*-butyl (2-hydroxy-1-phenylethyl)carbamate **15** and **A9**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **21g** as a colorless oil (19 mg, 27%): R_f 0.26 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$); δ 9.95 (s, 1H), 7.48-7.26 (m, 8H), 7.15 (dt, J = 7.5, 2.1 Hz, 1H), 5.29 (s(br), 1H), 5.08 (s(br), 1H), 4.31-4.19 (m, 2H), 1.43 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 192.0, 159.0, 155.3, 139.4, 137.8, 130.2, 128.7, 127.8, 126.8, 123.9, 121.8, 113.2, 80.0, 70.9, 53.9, 28.4; IR (neat) 3355, 3085, 3056, 2976, 2931, 2740, 1689, 1596, 1585, 1484, 1451, 1251, 1164, 1050; HRMS (ESI) calcd for $C_{20}H_{23}NO_4$: 341.1627, found 364.1529 (M+Na).

(*R*,*E*)-Ethyl 3-(3-(2-((*tert*-butoxycarbonyl)amino)-2-phenylethoxy)phenyl)acrylate (21h)

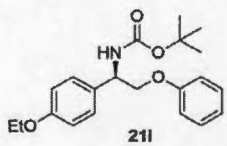


21h

Method A was followed on a 0.08 mmol scale starting from *(R)-tert*-butyl (2-hydroxy-1-phenylethyl)carbamate **15** and **A10**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **21h** as a colorless oil (23 mg, 70%): R_f 0.30 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$); δ 7.63 (d, J = 15.9 Hz, 1H), 7.42-7.26 (m, 6H), 7.12 (d, J = 7.7 Hz, 1H), 7.05 (s, 1H), 6.91 (dd, J = 8.2, 1.9 Hz, 1H), 6.43 (d, J = 15.9 Hz, 1H), 5.31 (s(br), 1H), 5.08 (s(br), 1H), 4.30-4.16 (m, 4H), 1.45 (s, 9H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.9, 158.8, 155.3, 144.3, 135.9, 129.9, 128.7, 127.8, 126.8, 121.4, 118.8, 116.7, 113.7, 80.0, 70.7, 60.5, 28.4, 14.3; IR (neat) 3351, 3071, 3048, 2977, 2932, 1700, 1637, 1579, 1492, 1445, 1365, 1245, 1159, 1030; HRMS (ESI) calcd for $C_{24}H_{29}NO_5$: 411.2046, found 434.1941 (M+Na).

P. Petiot, J. Dansereau, M. Hébert, I. Khene, T. Ahmad, S. Samaali, M. Leroy, F. Pinsonneault, C. Y. Legault and A. Gagnon

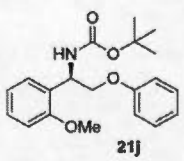
(*R*)-*tert*-Butyl (1-(4-ethoxyphenyl)-2-phenoxyethyl)carbamate (21i)



21i

Method B was followed on a 0.18 mmol scale starting from (*R*)-*tert*-butyl (1-(4-ethoxyphenyl)-2-hydroxyethyl)carbamate and **A1**. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford **21i** as a white solid (26 mg, 40%): m.p. 125°C; R_f 0.40 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34-7.27 (m, 4H), 6.98 (t, J = 7.3 Hz, 1H), 6.93-6.87 (m, 4H), 5.29 (s(br), 1H), 5.02 (s(br), 1H), 4.25-4.20 (m, 1H), 4.17-4.15 (m, 1H), 4.04 (q, J = 7.0 Hz, 2H), 1.46-1.41 (m, 12H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.4, 155.4, 131.8, 129.5, 128.0, 121.2, 115.4, 114.6, 114.5, 79.8, 70.6, 63.5, 28.4, 14.9; IR (neat) 3350, 3065, 3034, 2977, 2930, 2875, 1694, 1501, 1496, 1238, 1164, 1046, 754.

(*R*)-*tert*-Butyl (1-(2-methoxyphenyl)-2-phenoxyethyl)carbamate (21j)

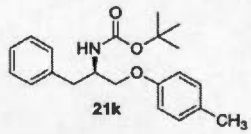


21j

Method B was followed on a 0.13 mmol scale starting from (*R*)-*tert*-butyl (2-hydroxy-1-(2-methoxyphenyl)ethyl)carbamate and **A1**. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford **21j** as a white solid (17 mg, 38%): m.p. 104°C; R_f 0.38 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35-7.22 (m, 4H), 7.00-6.95 (m, 2H), 6.89 (dd, J = 8.8, 3.7 Hz, 3H), 5.62 (s(br), 1H), 5.39 (s(br), 1H), 4.24 (dd, J = 9.5, 5.1 Hz, 1H), 4.17-4.12 (m, 1H), 3.88 (s, 3H), 1.47 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.6, 156.8, 155.4, 129.6, 129.4, 128.7, 128.5, 120.9, 120.7, 115.3, 114.7, 110.6, 79.6, 69.4, 55.3, 50.8, 28.4; IR (neat) 3444, 3361, 3061, 3038, 2975, 2933, 2837, 1701, 1600, 1492, 1461, 1365, 1240, 1166, 752.

P. Petiot, J. Dansereau, M. Hébert, I. Khene, T. Ahmad, S. Samaali, M. Leroy, F. Pinsonneault, C. Y. Legault and A. Gagnon

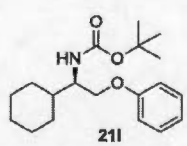
(*R*)-*tert*-Butyl (1-phenyl-3-(*p*-tolyloxy)propan-2-yl)carbamate (21k)



21k

Method A was followed on a 0.20 mmol scale starting from *(R)-tert*-butyl (2-hydroxy-1-phenylethyl)carbamate and **A3**. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford **21k** as a yellow solid (33 mg, 48%): m.p. 69°C; R_f 0.54 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.33-7.24 (m, 5H), 7.11 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 5.00 (s(br), 1H), 4.17 (s(br), 1H), 3.92-3.84 (m, 2H), 3.02 (d, J = 7.7 Hz, 2H), 2.33 (s, 3H), 1.47 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 156.5, 155.3, 137.9, 130.3, 130.0, 129.5, 128.5, 126.5, 114.4, 79.5, 67.8, 51.4, 37.8, 28.4, 20.5; IR (neat) 3452, 3350, 3061, 3028, 2976, 2925, 2868, 1710, 1510, 1238, 1165, 1039, 700; HRMS (ESI) calcd for $C_{21}H_{27}NO_3$: 341.1991, found 364.1879 (M+Na).

(*R*)-*tert*-Butyl (1-cyclohexyl-2-phenoxyethyl)carbamate (21l)

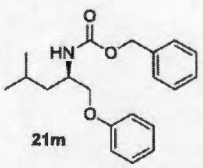


21l

Method A was followed on a 0.20 mmol scale starting from *tert*-butyl (*1R*)-1-cyclohexyl-2-hydroxyethylcarbamate and **A1**. The crude material was purified on silica gel (8% EtOAc/hexanes) to afford **21l** as a white solid (39 mg, 60%): m.p. 130°C; R_f 0.31 (10% AcOEt/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.31-7.26 (m, 2H), 6.98-6.93 (m, 1H), 6.91-6.88 (m, 2H), 4.85 (d, J = 9.4 Hz, 1H), 4.06 (dd, J = 9.4, 3.2 Hz, 1H), 3.95 (dd, J = 9.4, 3.8 Hz, 1H), 3.74-3.68 (m, 1H), 1.89-1.66 (m, 6H), 1.45 (s, 9H), 1.26-1.01 (m, 5H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 158.8, 155.8, 129.5, 120.9, 114.5, 79.2, 67.7, 54.5, 39.0, 29.9, 29.3, 28.4, 26.3, 26.1, 24.7; IR (neat) 3392, 3008, 2965, 2931, 2847, 1686, 1601, 1498, 1467, 1239, 1167, 1152, 753, 692; HRMS (ESI) calcd for $C_{19}H_{29}NO_3$: 319.2147, found 342.2025 (M+Na).

P. Petiot, J. Dansereau, M. Hébert, I. Khene, T. Ahmad, S. Samaali, M. Leroy, F. Pinsonneault, C. Y. Legault and A. Gagnon

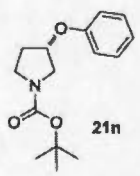
Benzyl (*R*)-(4-methyl-1-phenoxypentan-2-yl)carbamate (21m)



21m

Method A was followed on a 0.20 mmol scale starting from benzyl (*R*)-(1-hydroxy-4-methylpentan-2-yl)carbamate and **A1**. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford **21m** as a colorless oil (32 mg, 49%): R_f 0.55 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.41-7.29 (m, 7H), 7.03-6.88 (m, 3H), 5.16 (s, 2H), 5.03 (d, J = 8.5 Hz, 1H), 4.19-3.97 (m, 3H), 1.80-1.68 (m, 1H), 1.63-1.54 (m, 2H), 1.00 (d, J = 6.5 Hz, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.7, 156.0, 136.5, 129.6, 129.5, 128.6, 128.1, 121.0, 115.3, 114.5, 69.8, 66.8, 48.9, 41.0, 36.7, 24.8, 23.0, 22.3; IR (neat) 3324, 3065, 3038, 2955, 2869, 1695, 1599, 1513, 1496, 1237, 753; HRMS (ESI) calcd for $C_{20}H_{25}NO_3$: 327.1834, found 328.1922 (M+H).

(*S*)-*tert*-Butyl 3-phenoxypyrrolidine-1-carboxylate (21n)

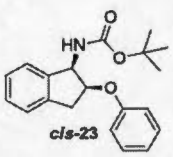


21n

Method B was followed on a 0.27 mmol scale starting from (*S*)-*tert*-butyl 3-hydroxypyrrolidine-1-carboxylate and **A1**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **21n** as a yellow oil (37 mg, 52%): R_f 0.46 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.31-7.28 (m, 2H), 7.00-6.98 (m, 1H), 6.89 (d, J = 8.0 Hz, 2H), 4.90 (s, 1H), 3.65-3.55 (m, 4H), 2.18-2.06 (m, 2H), 1.49 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 157.2, 154.6, 129.6, 121.1, 115.6, 79.4, 76.3, 75.5, 51.7, 51.4, 44.1, 43.8, 31.5, 30.8, 28.5; IR (neat) 3069, 3038, 2975, 2881, 1690, 1599, 1587, 1494, 1401, 1364, 1237, 1164, 752; HRMS (ESI) calcd for $C_{15}H_{21}NO_3$: 263.1521, found 286.1420 (M+Na).

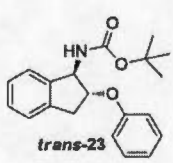
P. Petiot, J. Dansereau, M. Hébert, I. Khene, T. Ahmad, S. Samaali, M. Leroy, F. Pinsonneault, C. Y. Legault and A. Gagnon

tert-Butyl ((_1R,2S_)-2-phenoxy-2,3-dihydro-_1H_-inden-1-yl)carbamate (_cis_-23)



Method B was followed on a 0.20 mmol scale starting from *tert*-butyl ((*1R,2S*)-2-hydroxy-2,3-dihydro-*1H*-inden-1-yl)carbamate *cis*-**22** and **A1**. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford *cis*-**23** as a yellow solid (34 mg, 52%): m.p. 106°C; R_f 0.57 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.30-7.12 (m, 6H), 6.91-6.81 (m, 3H), 5.40-5.35 (m, 1H), 5.28-5.25 (m, 1H), 5.07 (s(br), 1H), 3.08 (d, J = 2.5 Hz, 2H), 1.40 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 157.6, 156.2, 141.7, 139.4, 129.6, 128.0, 127.2, 125.1, 124.1, 121.3, 115.8, 79.7, 78.8, 58.0, 36.9, 28.4; IR (neat) 3471, 3359, 3098, 3061, 2981, 2929, 1695, 1598, 1495, 1243, 1171, 1061; HRMS (ESI) calcd for $C_{20}H_{23}NO_3$: 325.1678, found 348.1578 (M+Na).

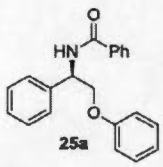
tert-Butyl ((_1R,2R_)-2-phenoxy-2,3-dihydro-_1H_-inden-1-yl)carbamate (_trans_-23)



Method B was followed on a 0.20 mmol scale starting from *tert*-butyl ((*1R,2R*)-2-hydroxy-2,3-dihydro-*1H*-inden-1-yl)carbamate *trans*-**22** and **A1**. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford *trans*-**23** as a white solid (45 mg, 69%): m.p. 115°C; R_f 0.46 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.39-7.24 (m, 6H), 7.06-6.98 (m, 3H), 5.32 (s(br), 1H), 4.96-4.91 (m, 1H), 4.84 (s(br), 1H), 3.51 (dd, J = 16.4, 6.5 Hz, 1H), 3.04 (dd, J = 16.4, 4.8 Hz, 1H), 1.50 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.0, 155.4, 140.6, 139.9, 129.5, 128.6, 127.4, 125.1, 124.6, 121.1, 115.8, 83.8, 79.8, 61.4, 36.9, 28.4; IR (neat) 3338, 3089, 3050, 2974, 2875, 1689, 1519, 1493, 1235, 1166, 1055, 746; HRMS (ESI) calcd for $C_{20}H_{23}NO_3$: 325.1678, found 348.1562 (M+Na).

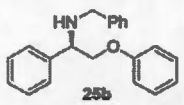
P. Petiot, J. Dansereau, M. Hébert, I. Khene, T. Ahmad, S. Samaali, M. Leroy, F. Pinsonneault, C. Y. Legault and A. Gagnon

(*R*)-*N*-(2-Phenoxy-1-phenylethyl)benzamide (25a)



Method B was followed on a 0.083 mmol scale starting from *(R)*-*N*-(2-hydroxy-1-phenylethyl)benzamide **24a** and **A1**. The crude product was purified on silica gel (15% EtOAc/hexanes) to afford **25a** as a white solid (18 mg, 68%): m.p. 123°C; R_f 0.25 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.83-7.80 (m, 2H), 7.54-7.26 (m, 9H), 7.01-6.92 (m, 4H), 5.64-5.58 (m, 1H), 4.42-4.33 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.1, 158.4, 139.3, 131.7, 129.6, 128.8, 128.7, 127.9, 127.1, 127.0, 121.5, 114.7, 70.0, 52.9; IR (neat) 3446, 3295, 3061, 3030, 2925, 2873, 1634, 1537, 1491, 1239, 1042, 691; HRMS (ESI) calcd for $C_{21}H_{19}NO_2$: 317.1416, found 318.1478 (M+H).

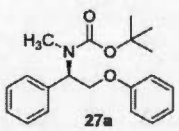
(*R*)-*N*-Benzyl-2-phenoxy-1-phenylethanamine (25b)



Method B was followed on a 0.22 mmol scale starting from *(R)*-2-(benzylamino)-2-phenylethanol **24b** and **A1**. The crude product was purified on silica gel (5% EtOAc/hexanes) to afford **25b** as a yellow oil (43 mg, 64%): R_f 0.60 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.55-7.52 (m, 2H), 7.45-7.24 (m, 10H), 6.99-6.88 (m, 3H), 4.21 (dd, J = 8.9, 3.8 Hz, 1H), 4.10-3.99 (m, 2H), 3.78 (d, J = 13.2 Hz, 1H), 3.65 (d, J = 13.3 Hz, 1H), 2.33 (s(br), 1H); ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.51-7.26 (m, 12H), 6.97-6.92 (m, 3H), 4.10-4.03 (m, 3H), 3.68 (d, J = 13.6 Hz, 1H), 3.55 (d, J = 13.6 Hz, 1H), 2.76 (s(br), 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.6, 140.5, 140.1, 129.5, 128.7, 128.4, 128.1, 127.9, 127.8, 126.9, 121.0, 114.7, 72.8, 61.8, 51.4; IR (neat) 3304, 3057, 3023, 2912, 2848, 1597, 1494, 1448, 1323, 1238, 1144, 752; HRMS (ESI) calcd for $C_{21}H_{21}NO$: 303.1623, found 304.1700 (M+H). To further confirm the chemoselectivity of the reaction and the structure of the

compound, we compared the data with the *N*-phenyl isomer from the literature and found the two compounds to be different.[8]

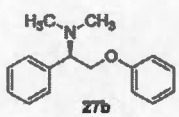
(*R*)-*tert*-Butyl methyl(2-phenoxy-1-phenylethyl)carbamate (27a)



27a

Method B was followed on a 0.20 mmol scale starting from *(R)-tert*-butyl (2-hydroxy-1-phenylethyl)(methyl)carbamate **26a** and **A1**. The crude product was purified on silica gel (5% EtOAc/hexanes) to afford **27a** as a yellow oil (43 mg, 66%): R_f 0.60 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.26 (m, 7H), 7.00-6.94 (m, 3H), 5.58 (s, 1H), 4.48-4.36 (m, 2H), 2.76 (s, 3H), 1.46 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.5, 138.0, 129.5, 128.6, 127.6, 127.5, 127.3, 127.2, 121.2, 114.8, 79.9, 67.0, 29.7, 28.4; IR (neat) 3063, 3031, 2975, 2928, 1690, 1599, 1496, 1390, 1243, 1146, 754; HRMS (ESI) calcd for $C_{20}H_{25}NO_3$: 327.1834, found 350.1720 (M+Na).

(*R*)-*N*,*N*-Dimethyl-2-phenoxy-1-phenylethanamine (27b)

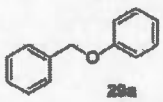


27b

Method B was followed on a 0.24 mmol scale starting from *(R)*-2-(dimethylamino)-2-phenylethanol **26b** and **A1**. The crude product was purified on silica gel (5% EtOAc/hexanes) to afford **27b** as a yellow oil (42 mg, 73%): R_f 0.32 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.33 (d, J = 4.4 Hz, 4H), 7.30-7.21 (m, 3H), 6.93-6.85 (m, 3H), 4.30 (dd, J = 10.0, 6.1 Hz, 1H), 4.18 (dd, J = 10.0, 4.8 Hz, 1H), 3.60 (t, J = 5.2 Hz, 1H), 2.29 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.7, 139.4, 129.4, 128.4, 128.3, 127.6, 120.9, 114.8, 69.9, 69.7, 43.6; IR (neat) 3061, 3029, 2948, 2866, 2821, 2774, 1598, 1586, 1495, 1469, 1454, 1238, 1041, 752, 691; HRMS (ESI) calcd for $C_{16}H_{19}NO$: 241.1467, found 242.1542 (M+H).

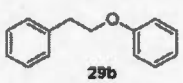
P. Petiot, J. Dansereau, M. Hébert, I. Khene, T. Ahmad, S. Samaali, M. Leroy, F. Pinsonneault, C. Y. Legault and A. Gagnon

Benzyloxybenzene (29a)



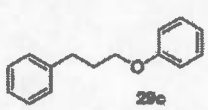
Method B was followed on a 0.46 mmol scale starting from phenylmethanol **28a** and **A1**. The crude material was purified on silica gel (heptane) to afford **29a** as a yellow oil (29 mg, 34%): R_f 0.73 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.48-7.26 (m, 7H), 7.02-6.96 (m, 3H), 5.09 (s, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.8, 137.1, 129.5, 128.6, 128.0, 127.5, 121.0, 114.9, 70.0; IR (neat) 3064, 3032, 2918, 1598, 1495, 1454, 1240, 1029, 752; HRMS (ESI) calcd for $C_{13}H_{12}O$: 184.0888, found 185.0967 (M+H).

Phenethoxybenzene (29b)



Method B was followed on a 0.41 mmol scale starting from 2-phenylethanol **28b** and **A1**. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford **29b** as a colorless oil (35 mg, 43%): R_f 0.75 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.39-7.27 (m, 7H), 7.01-6.93 (m, 3H), 4.22 (t, J = 7.1 Hz, 2H), 3.15 (t, J = 7.1 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.8, 138.3, 129.5, 129.0, 128.5, 126.5, 120.8, 114.6, 68.6, 35.8; IR (neat) 3063, 3028, 2927, 2870, 1597, 1586, 1497, 1472, 1243, 1037, 752; HRMS (ESI) calcd for $C_{14}H_{14}O$: 198.1045, found 199.1111 (M+H).

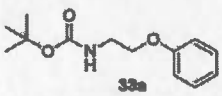
3-Phenoxypropylbenzene 29c



Method B was followed on a 0.37 mmol scale starting from 3-phenylpropan-1-ol **28c** and **A1**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **29c** as a yellow oil (34 mg, 43%): R_f 0.79 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.38-7.23 (m, 7H), 7.03-6.95 (m, 3H), 4.03 (t, J

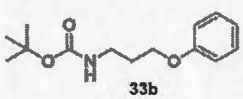
= 6.3 Hz, 2H), 2.88 (t, J = 7.3 Hz, 2H), 2.22-2.13 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 159.1, 141.6, 129.5, 128.6, 128.5, 126.0, 120.6, 114.6, 66.8, 32.2, 30.9; IR (neat) 3062, 3027, 2927, 2869, 1600, 1586, 1497, 1469, 1245, 1039, 751, 691; HRMS (ESI) calcd for $C_{15}H_{16}O$: 212.1201, found 213.1277 (M+H).

***tert*-Butyl (2-phenoxyethyl)carbamate 33a**


33a

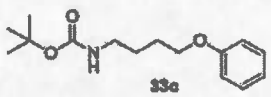
Method A was followed on a 0.31 mmol scale starting from *tert*-butyl (2-hydroxyethyl)carbamate **32a** and **A1**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **33a** as a colorless oil (38 mg, 52%): R_f 0.47 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34-7.28 (m, 2H), 7.01-6.96 (m, 1H), 6.93-6.90 (m, 2H), 5.07 (s(br), 1H), 4.04 (t, J = 5.1 Hz, 2H), 3.58-3.53 (m, 2H), 1.48 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.6, 156.0, 129.6, 121.1, 115.4, 114.5, 79.6, 67.1, 40.2, 28.4; IR (neat) 3351, 3057, 3038, 2976, 2932, 2875, 1693, 1599, 1587, 1496, 1274, 1241, 1164, 752; HRMS (ESI) calcd for $C_{13}H_{19}NO_3$: 237.1365, found 260.1256 (M+Na).

***tert*-Butyl (3-phenoxypropyl)carbamate 33b**


33b

Method A was followed on a 0.28 mmol scale starting from *tert*-butyl (3-hydroxypropyl)carbamate **32b** and **A1**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **33b** as a yellow solid (28 mg, 40%): m.p. 69°C; R_f 0.42 (20% EtOAc/hexanes), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.30 (dd, J = 8.3, 0.7 Hz, 2H), 6.97-6.90 (m, 3H), 4.82 (s(br), 1H), 4.04 (t, J = 5.9 Hz, 2H), 3.35 (q, J = 6.2 Hz, 2H), 2.07-1.96 (m, 2H), 1.47 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.8, 156.1, 129.5, 120.8, 114.5, 79.2, 65.7, 38.1, 29.5, 28.4; IR (neat) 3351, 3072, 3038, 2976, 2931, 2875, 1689, 1600, 1587, 1497, 1365, 1242, 1169, 753; HRMS (ESI) calcd for $C_{14}H_{21}NO_3$: 251.1521, found 274.1411 (M+Na).

***tert*-Butyl (4-phenoxybutyl)carbamate (33c)**



Method B was followed on a 0.26 mmol scale starting from *tert*-butyl (4-hydroxybutyl)carbamate **32c** and **A1**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **33c** as a colorless oil (29 mg, 42%): R_f 0.50 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.32-7.27 (m, 2H), 6.98-6.90 (m, 3H), 4.70 (s(br), 1H), 3.99 (t, J = 6.1 Hz, 2H), 3.21 (q, J = 6.4 Hz, 2H), 1.86-1.79 (m, 2H), 1.74-1.66 (m, 2H), 1.47 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.9, 156.1, 129.5, 120.7, 114.5, 79.1, 67.3, 40.3, 28.4, 26.9, 26.6; IR (neat) 3357, 3065, 3034, 2975, 2933, 2870, 1689, 1600, 1586, 1497, 1473, 1365, 1243, 1168, 753; HRMS (ESI) calcd for $C_{15}H_{23}NO_3$: 265.1678, found 288.1566 (M+Na).

5. Competition studies

Scheme 8. Competition studies between phenethylalcohol **28b** and (*R*)-*N*-*tert*-butyloxycarbonyl-2-phenylglycinol **15**:

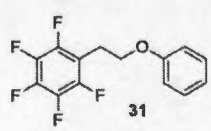
In a sealed tube, triphenylbismuth **A1** (0.41 mmol, 1.0 equiv) was added, followed by copper (II) acetate (1.0 equiv) and alcohol **28b** and **15** (1.0 equiv for each). The reagents were dissolved in anhydrous dichloromethane (5 mL) and pyridine (3.0 equiv) was added to the mixture. The reaction tube was purged with dry oxygen for 30 seconds, sealed and heated at 50°C overnight. The reaction mixture was cooled to r.t., concentrated under reduced pressure, and diluted with EtOAc. The organic layer was washed with aq. ammonium hydroxide (2x20mL), brine (1x20mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The NMR was taken on the obtained crude oil. The ratio of **29b** and **16** was determined by the

integration of signals corresponding to the benzylic C–H of **16**, and the benzylic CH_2 of **29b**, after correction for the number of protons.

Scheme 9. Competition studies between (pentafluorophenyl)ethanol **30** and (*R*)-*N*-*tert*-butyloxycarbonyl-2-phenylglycinol **15**:

In a sealed tube, triphenylbismuth **A1** (0.41 mmol, 1.0 equiv) was added, followed by copper (II) acetate (1.0 equiv) and alcohol **30** and **15** (1.0 equiv for each). The reagents were dissolved in anhydrous dichloromethane (5 mL) and pyridine (3.0 equiv) was added to the mixture. The reaction tube was purged with dry oxygen for 30 seconds, sealed and heated at 50°C overnight. The reaction mixture was cooled to r.t., concentrated under reduced pressure, and diluted with EtOAc. The organic layer was washed with aq. ammonium hydroxide (2x20mL), brine (1x20mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The NMR was taken on the obtained crude oil. The ratio of **31** and **16** was determined by the integration of signals corresponding to the benzylic C–H of **16** and the benzylic CH_2 of **31**, after correction for the number of protons.

1,2,3,4,5-Pentafluoro-6-(2-phenoxyethyl)benzene (31)



31

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.33-7.26 (m, 2H), 7.00-6.95 (m, 1H), 6.90-6.86 (m, 2H), 4.18 (t, J = 6.5 Hz, 2H), 3.22 (t, J = 6.5 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.3, 129.5, 121.2, 114.5, 111.6, 111.5, 111.3, 65.6, 29.7, 22.9; IR (neat) 3706, 3680, 3035, 2967, 2937, 2866, 1657, 1601, 1504, 1242, 1055, 752; HRMS (ESI) calcd for $C_{14}H_9F_5O$: 288.0571, found 289.0644 (M+H).

P. Petiot, J. Dansereau, M. Hébert, I. Khene, T. Ahmad, S. Samaali, M. Leroy, F. Pinsonneault, C. Y. Legault and A. Gagnon

6. Computational details

All calculations were performed with ORCA 3.0.1 software. The procedure reported by Pulay *et al.* was directly applied to the selected compounds for pK_a determination, using the equation described below.[9] The structures were fully optimized with the OLYP density functional[10] in combination with the 3-21G basis set for all atoms, using the COSMO solvation model for water.[11] Harmonic vibrational frequencies were computed for all optimized structures to verify that they were minima, possessing zero imaginary frequencies. The reported energies, used for pKa calculations, were obtained by single point calculations on the optimized structures using the OLYP density functional with the 6-311+G(d,p) basis set, again using the COSMO solvation model for water.

pK_a prediction equation for alcohols, as reported by Pulay et al.[9]

$pK_a = 0.3333 \cdot \Delta E - 90.447$

Table S2. Computed values for selected compounds.

Compound	E (Eh) anion (A^-)	E (Eh) neutral (HA)	ΔE (kcal/mol)	pK_a
15	-786,696005	-787,204025	318,787856	**15,8**
17b	-899,804801	-900,311973	318,255690	**15,6**
17d	-593,560154	-594,066536	317,759687	**15,5**
24a	-785,273340	-785,779612	317,690598	**15,4**
24b	-711,194933	-711,703171	318,924471	**15,9**
26a	-825,978949	-826,484095	316,984430	**15,2**
26b	-519,463652	-519,971521	318,692688	**15,8**
28b	-385,539151	-386,054130	323,154341	**17,3**
30	-881,759638	-882,266431	318,018046	**15,5**
32a	-555,685213	-556,189037	316,154172	**14,9**
32b	-594,981172	-595,491005	319,925776	**16,2**
32c	-634,276128	-634,786611	320,333426	**16,3**

7. References

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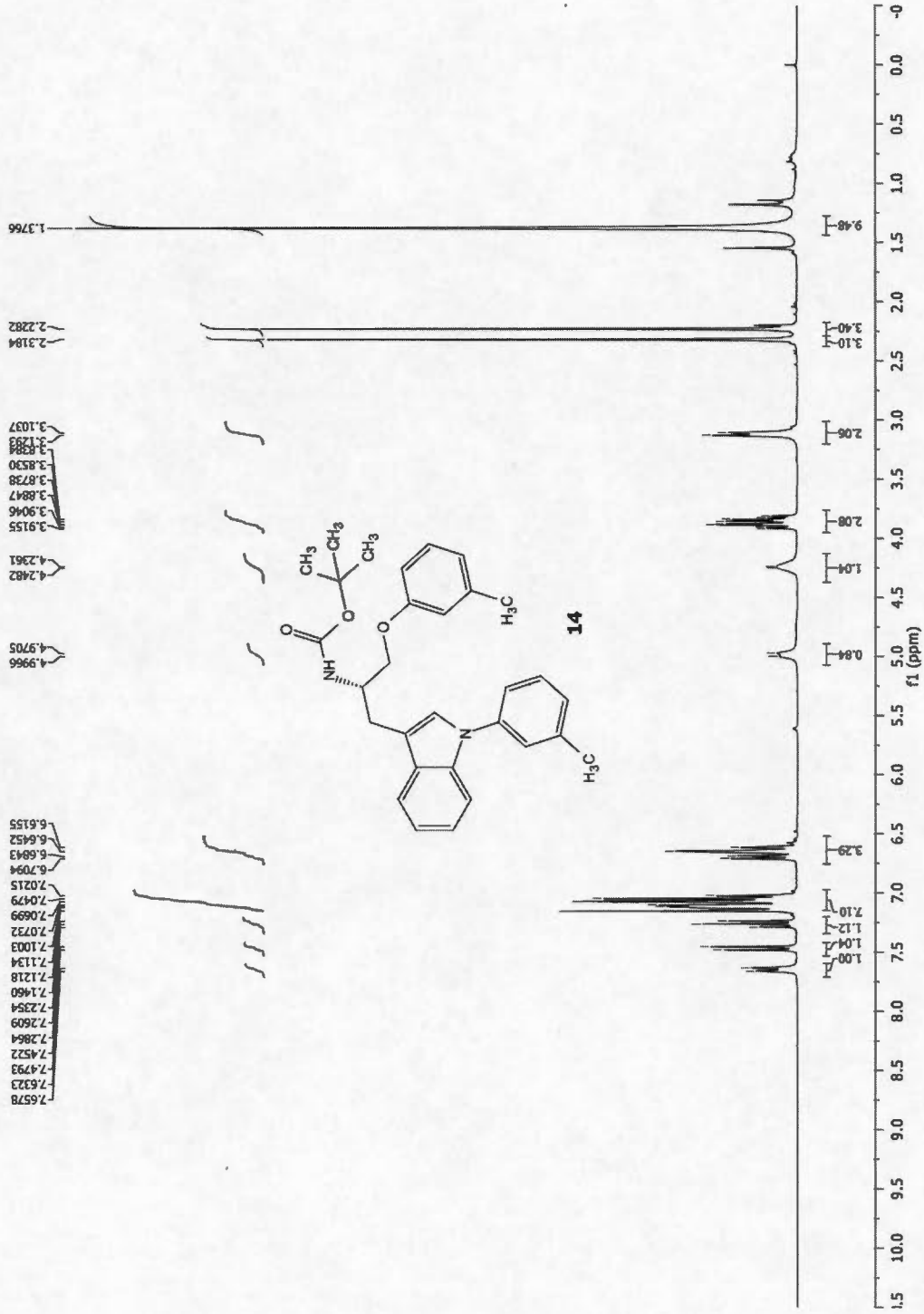
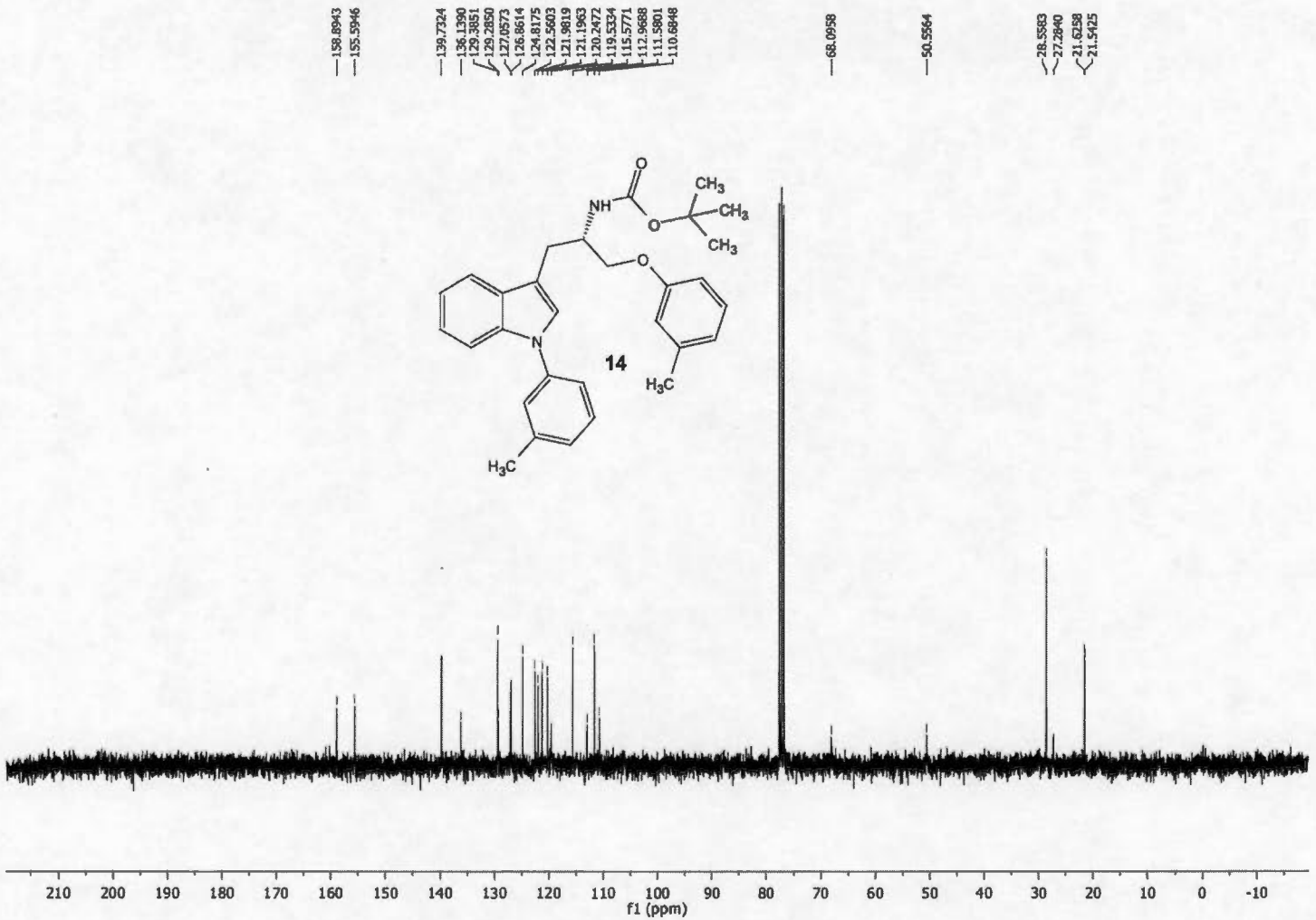

14
f1 (ppm)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136.1390
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122.5603
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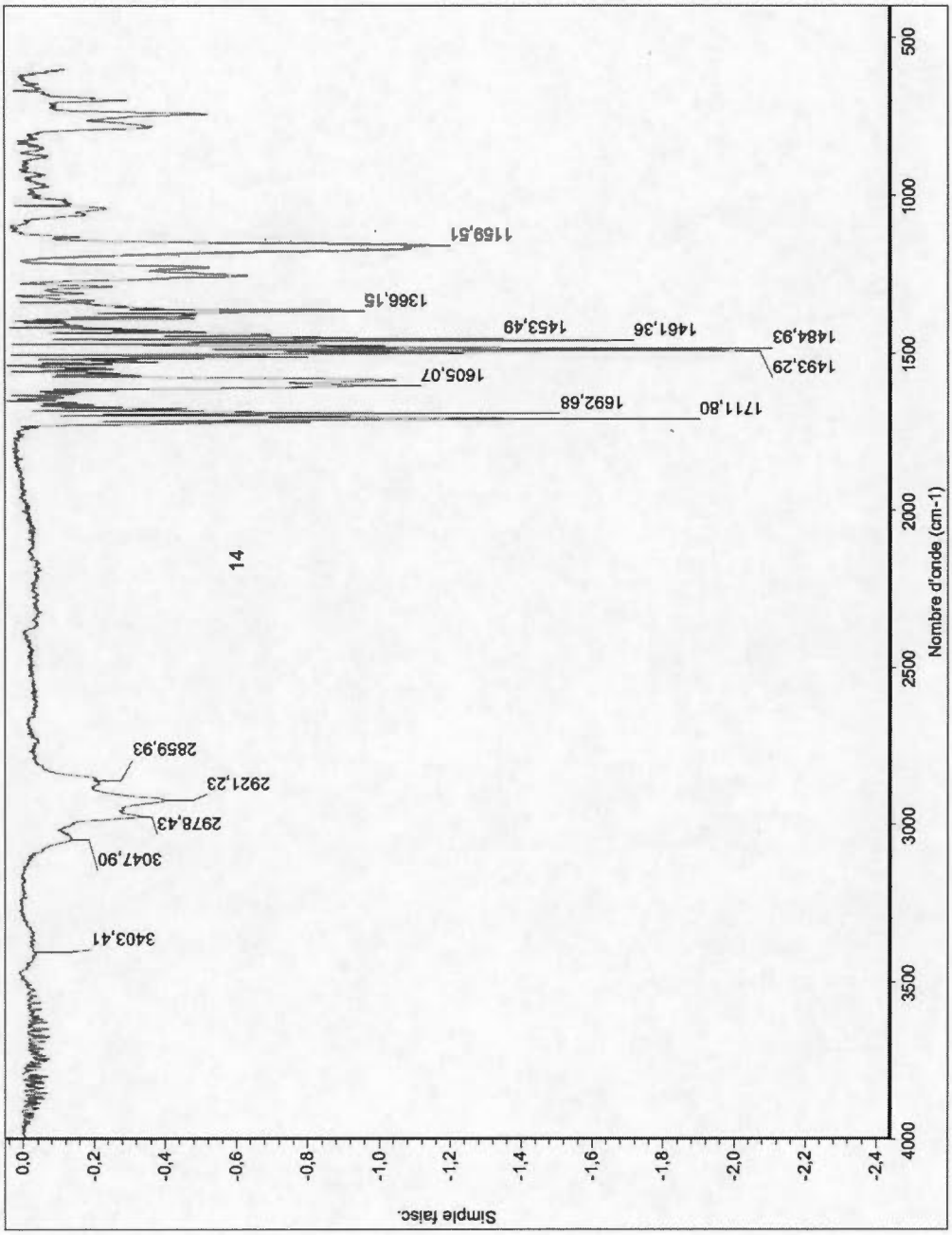
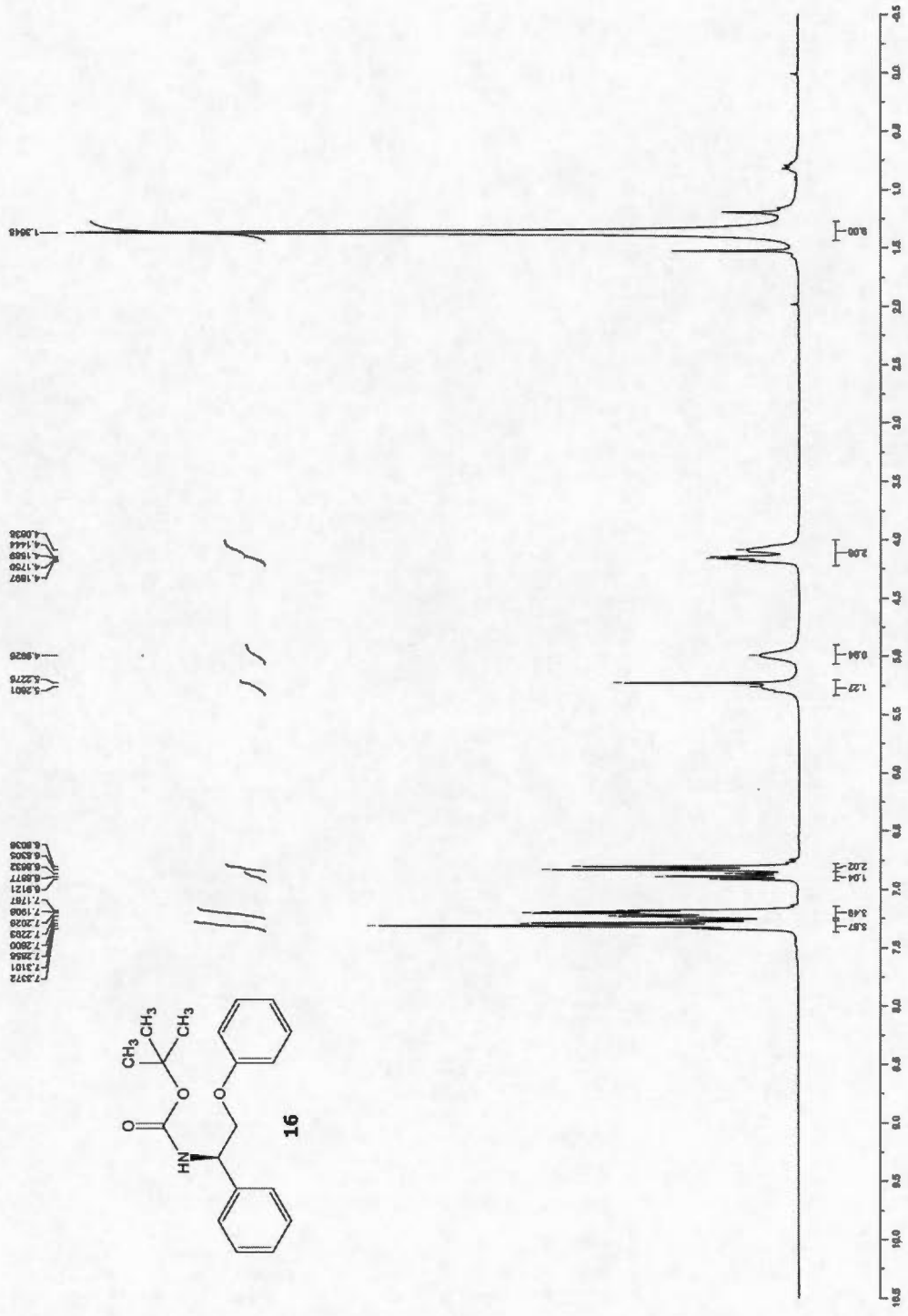
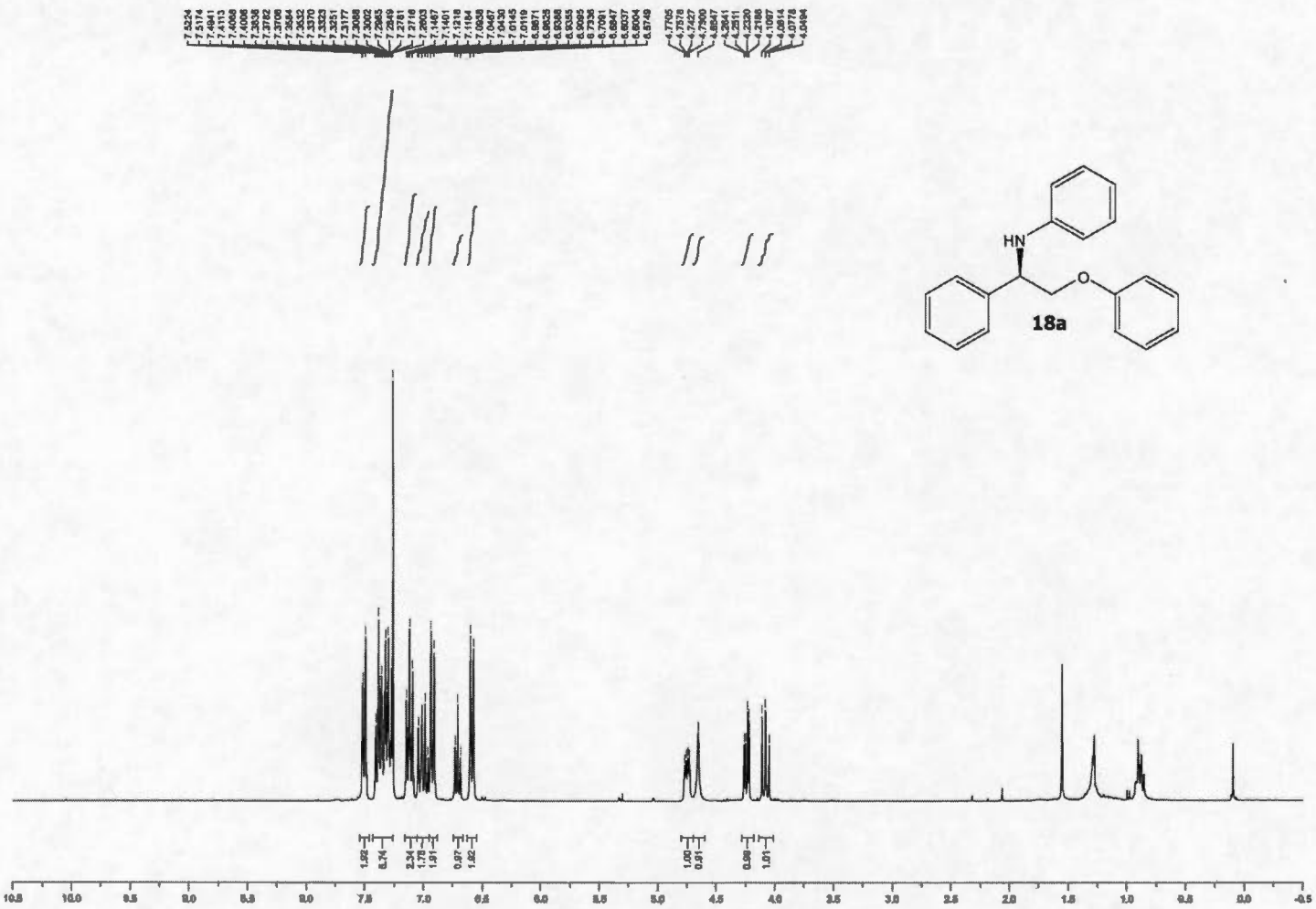
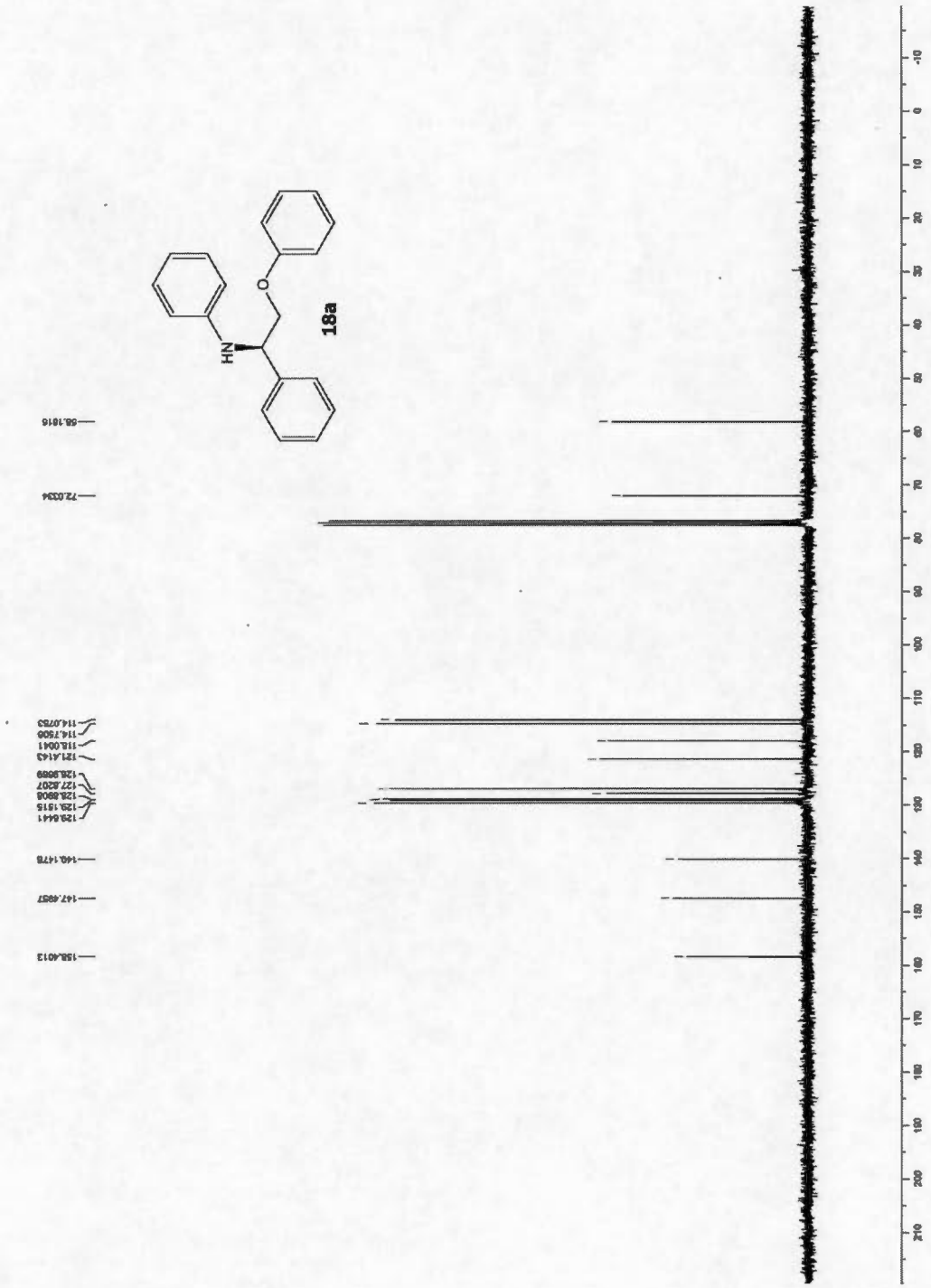
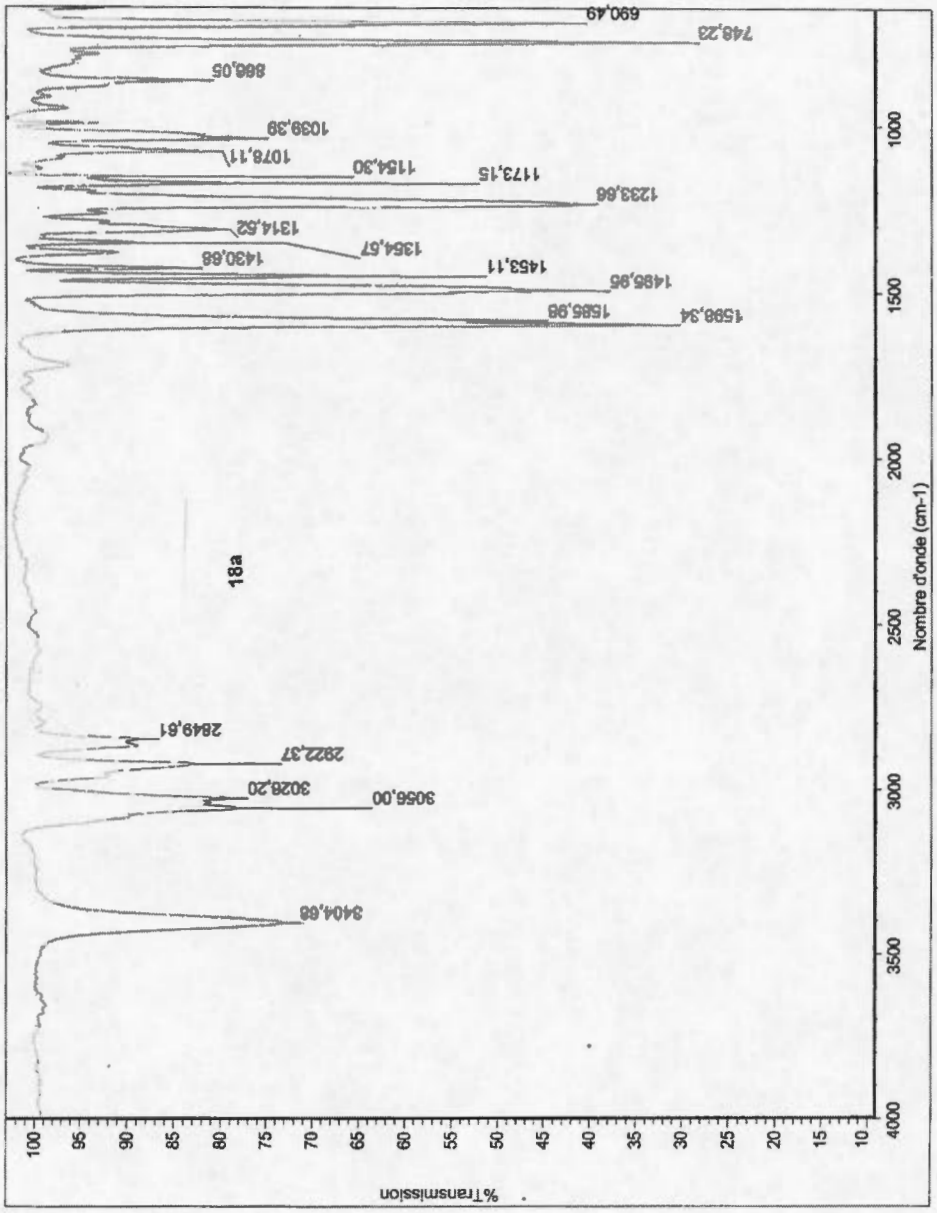
121.1963
120.2472
119.5334
115.5771
112.9688
111.5801
110.6848
68.0958
50.5564
28.5583
27.2840
21.6258
21.5425
NH
O
CH3
CH2
CH3
O
O
N
14
H3C
H3C
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

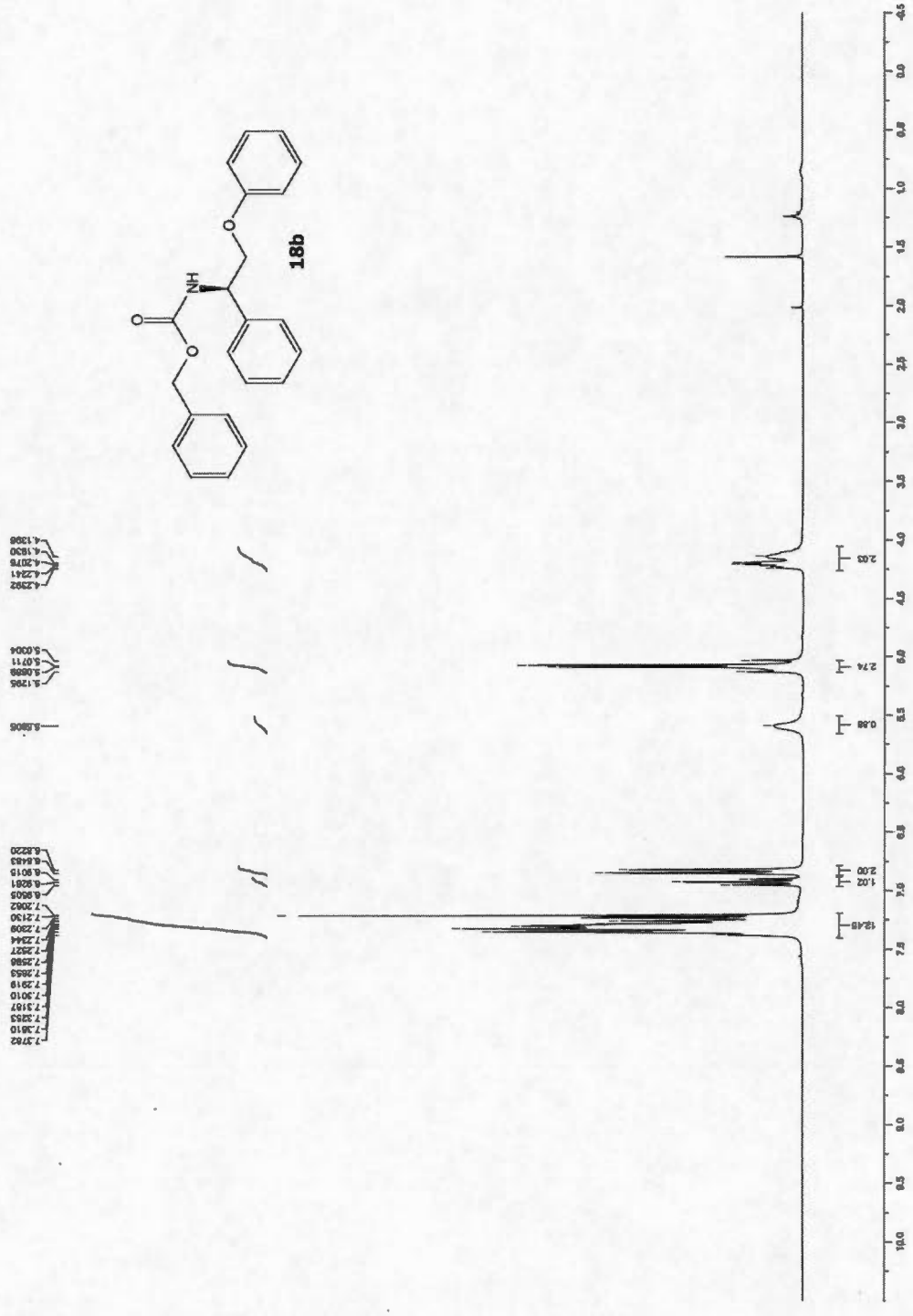

Simple faisc.
0,0
-0,2
-0,4
-0,6
-0,8
-1,0
-1,2
-1,4
-1,6
-1,8
-2,0
-2,2
-2,4
4000
3500
3000
2500
2000
1500
1000
500
Nombre d'onde (cm-1)
14
3403,41
3047,90
2978,43
2921,23
2859,93
1711,80
1692,68
1605,07
1493,29
1484,93
1461,36
1453,49
1366,15
1159,51

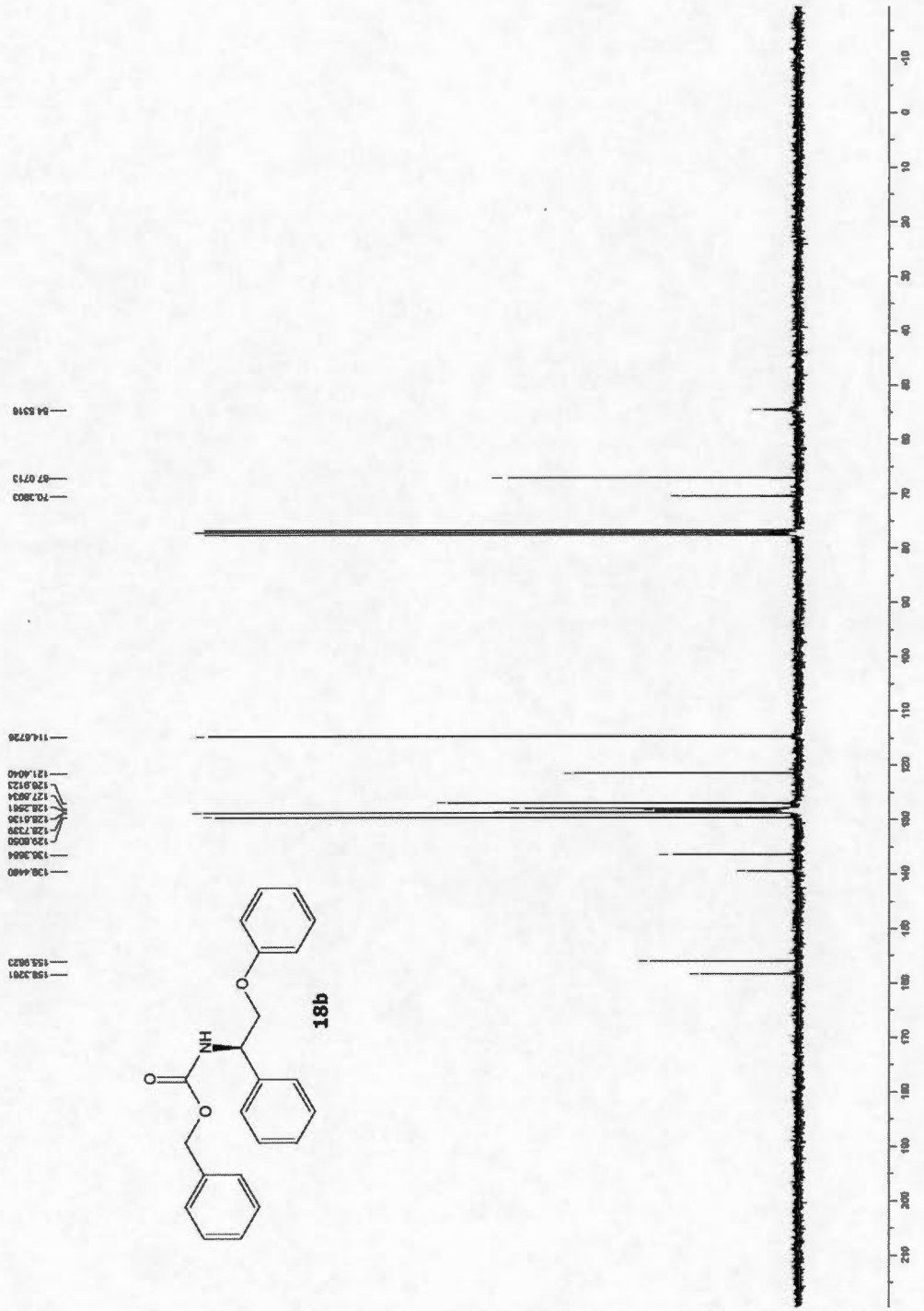

16

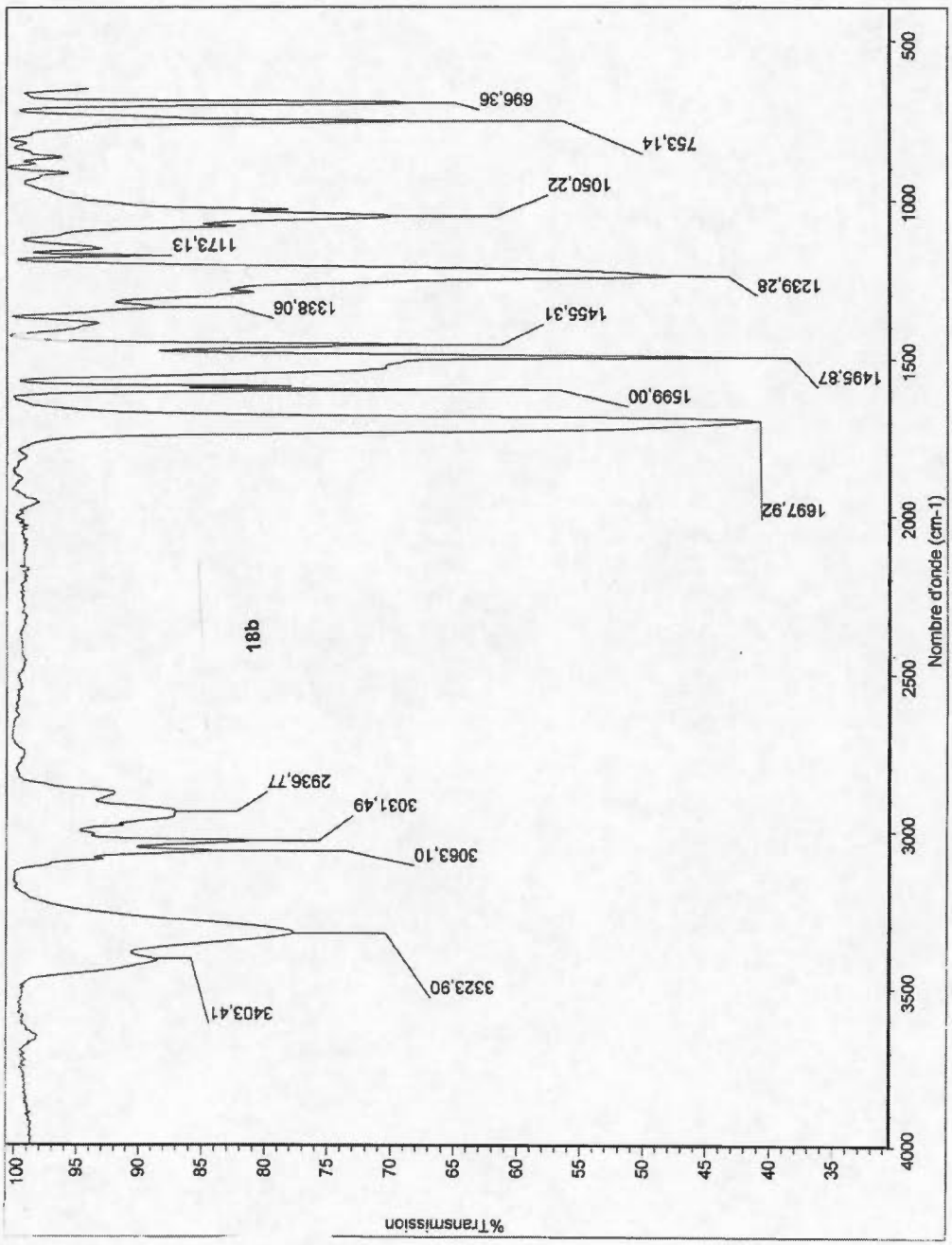

HN
O
18a

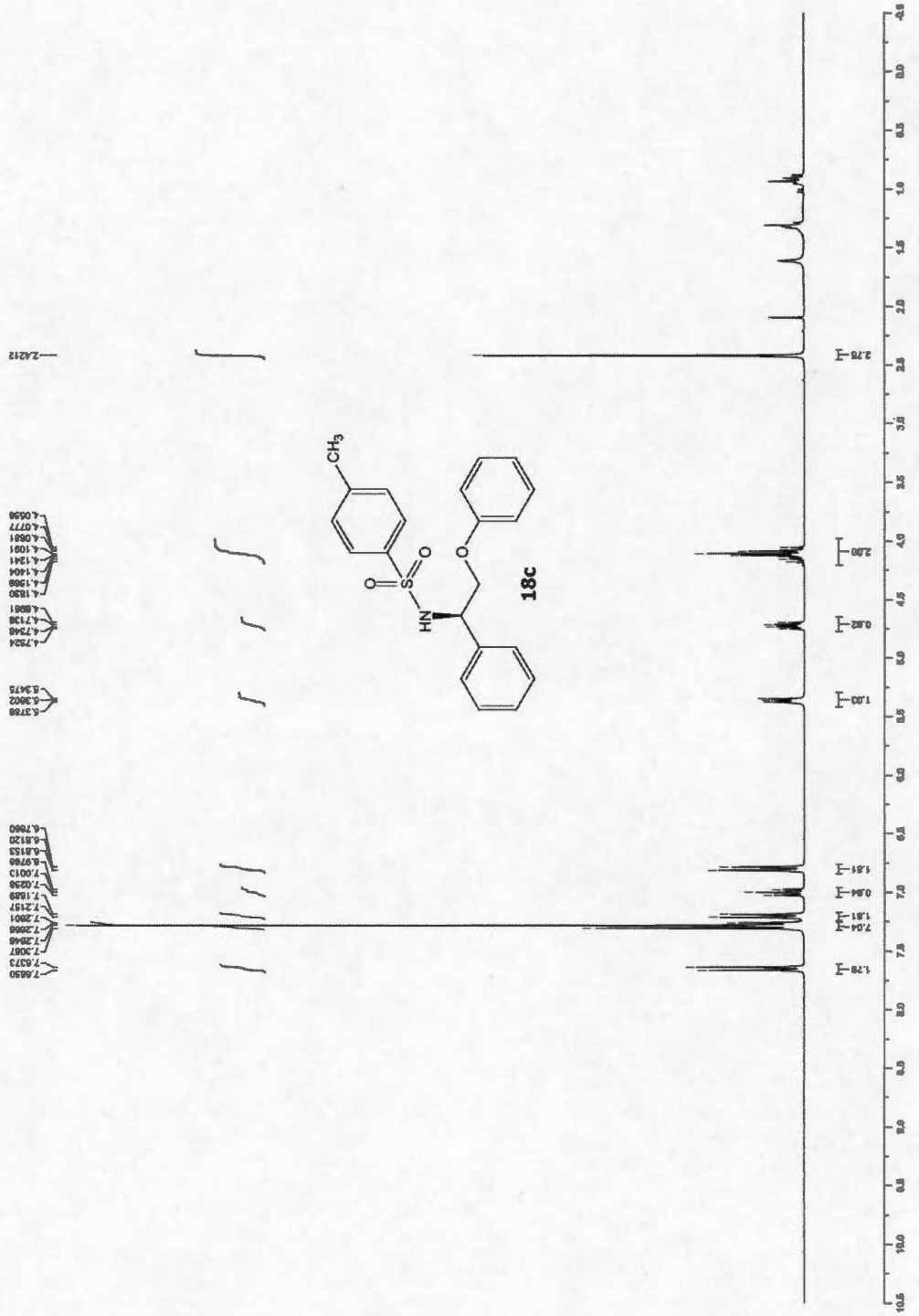

18a
HN
O
58.1816
72.0334
114.0783
114.7506
118.0041
121.4143
128.8089
127.8207
128.8906
129.1815
129.6441
140.1478
147.4857
158.4013

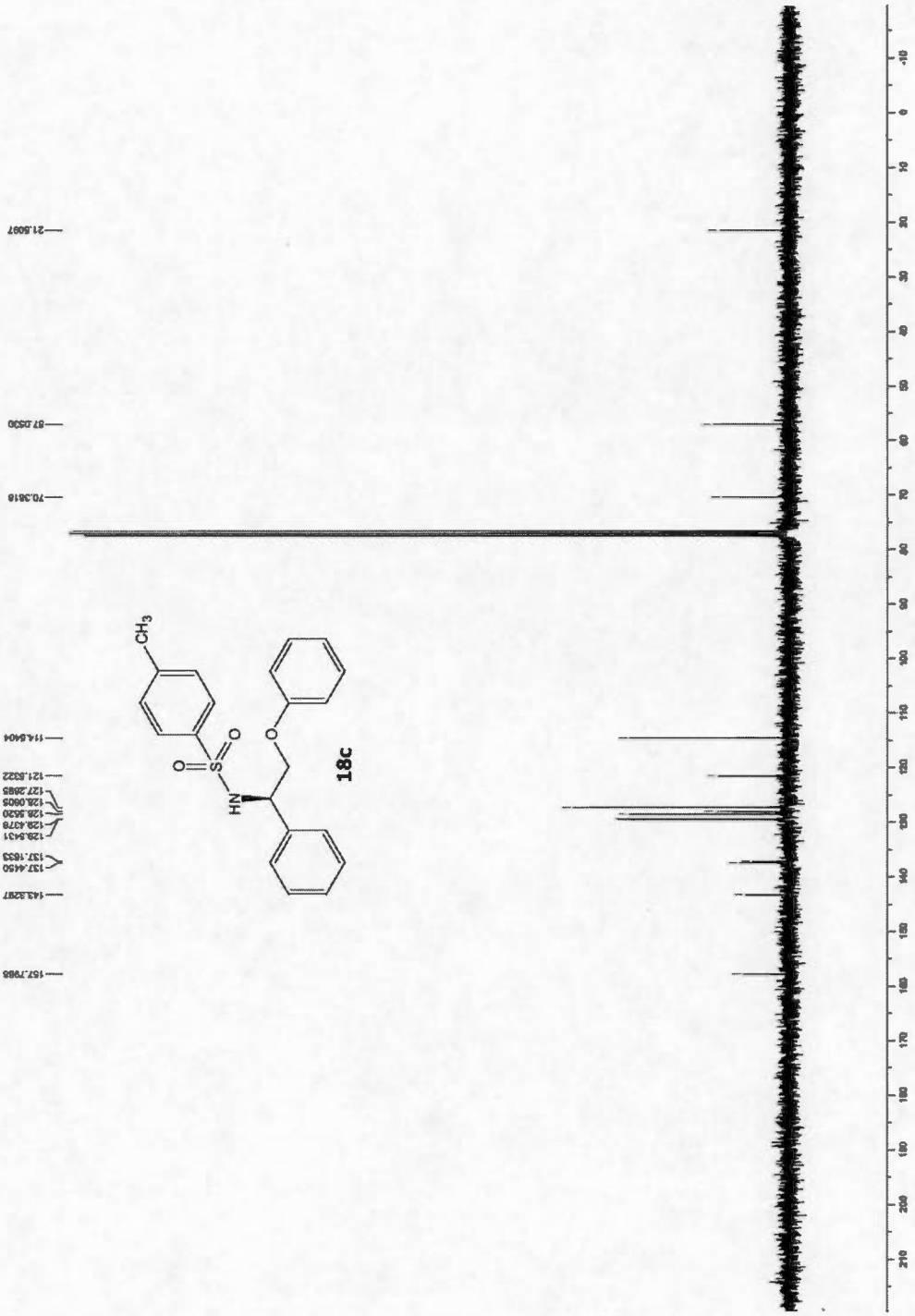

%Transmission
Nombre d'onde (cm-1)
18a
3404,68
3056,00
3028,20
2922,37
2849,61
1598,34
1585,98
1485,95
1453,11
1430,68
1364,67
1314,52
1233,66
1173,15
1154,30
1078,11
1039,39
886,05
748,23
690,49

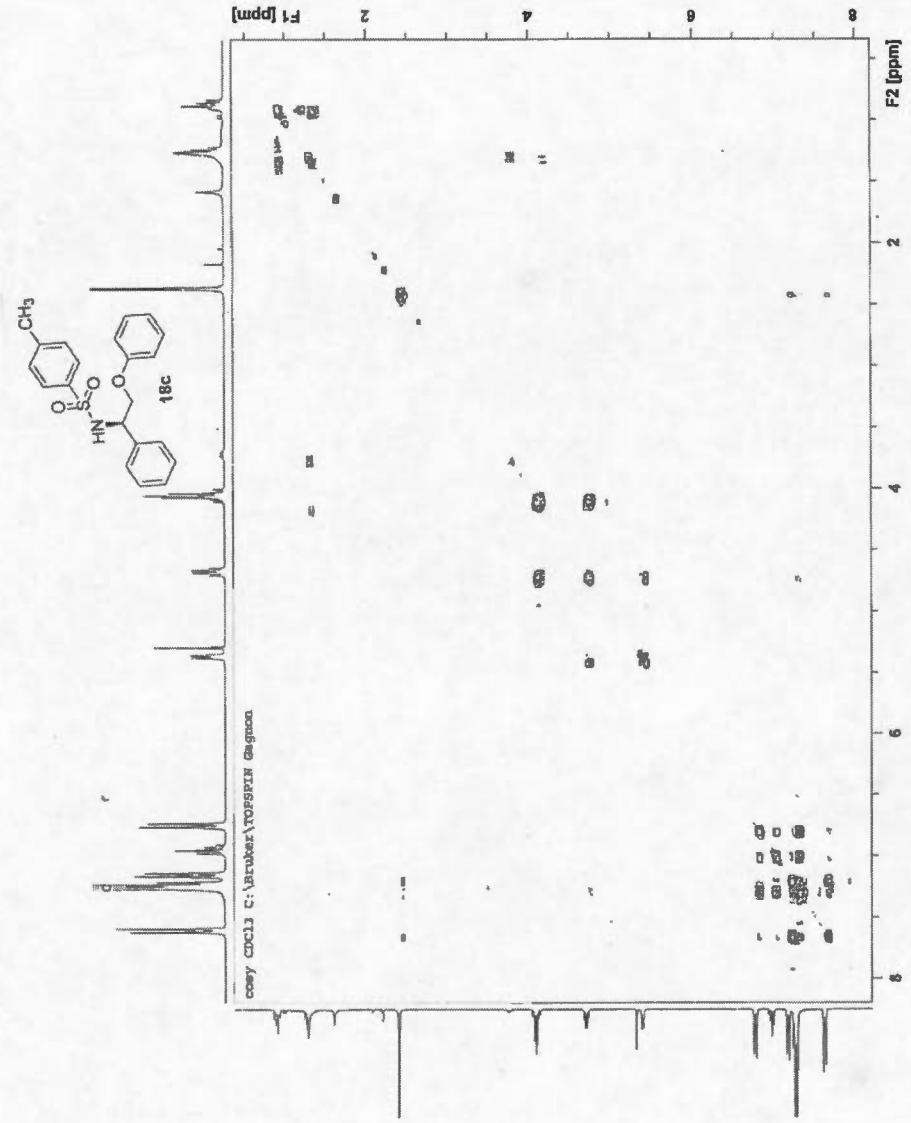

18b
NH
O
O
O
12.43
2.00
1.02
0.88
2.74
2.03

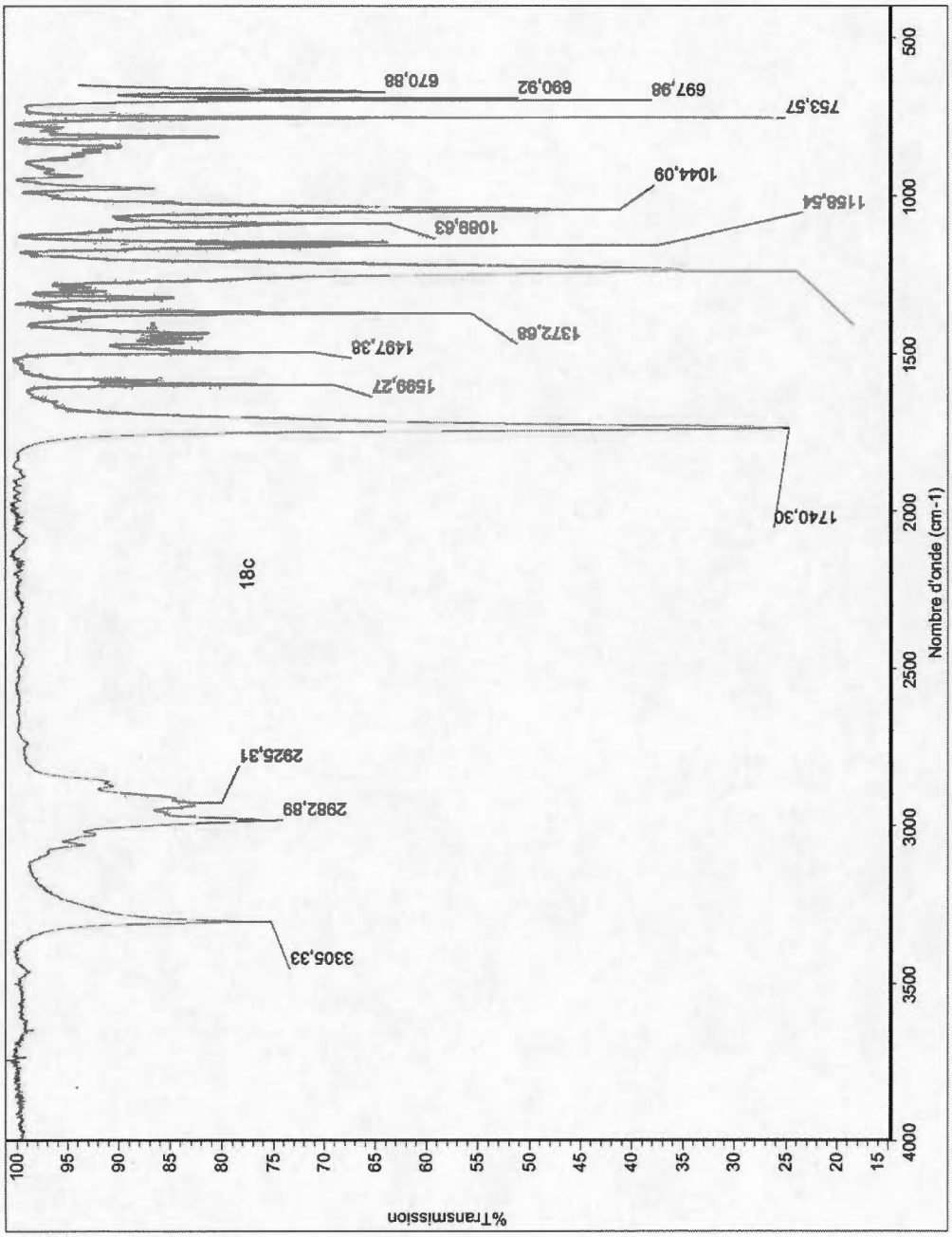

18b
NH
O
O
O
54.5316
67.0713
70.3803
114.6726
121.4040
128.0123
127.2834
128.2561
128.6136
128.7339
129.8050
136.3664
138.4460
155.3201
155.8023

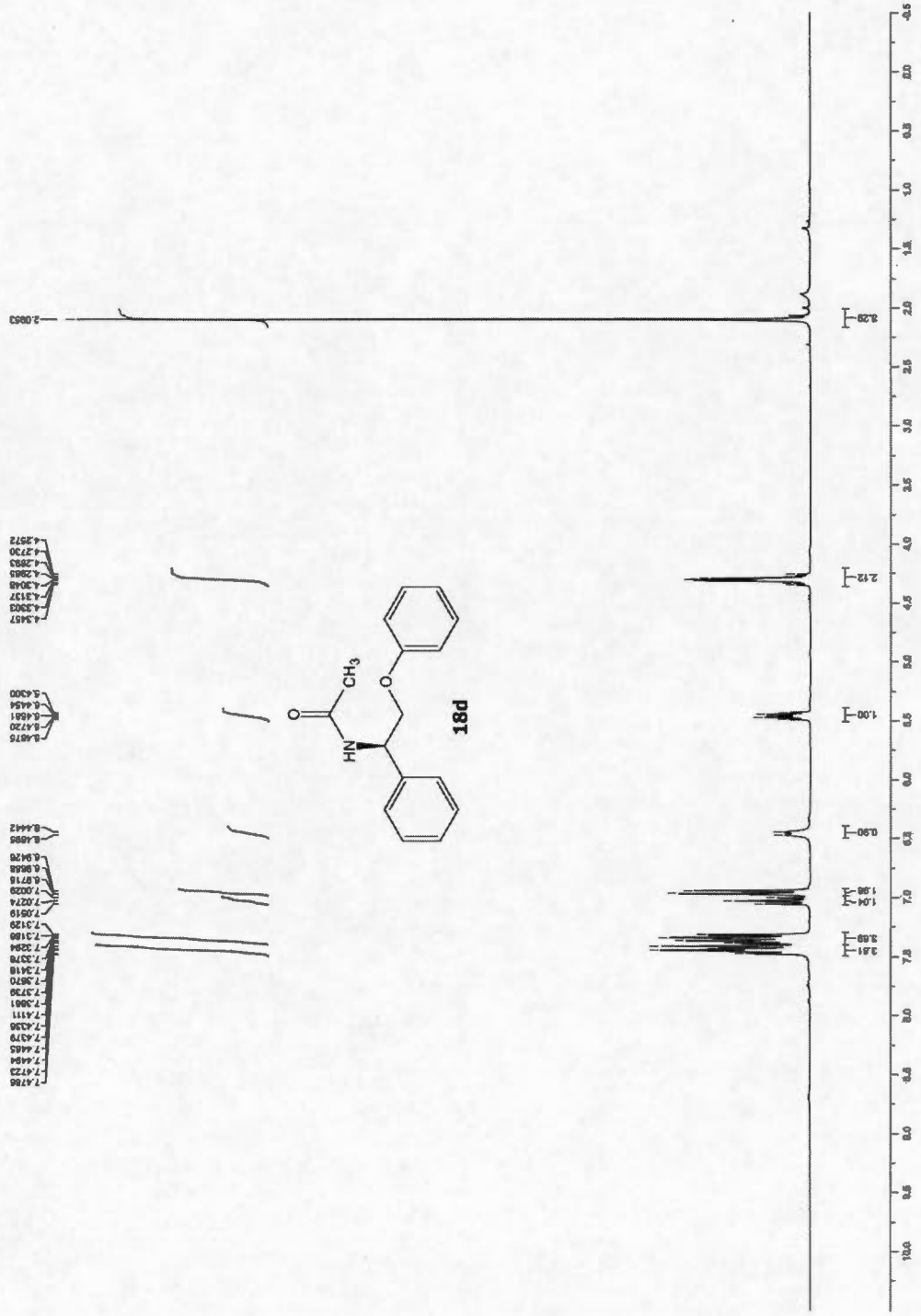

18b
%Transmission
Nombre d'onde (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
4000
3500
3000
2500
2000
1500
1000
500
3403,41
3323,90
3063,10
3031,49
2936,77
1697,92
1599,00
1495,87
1455,31
1338,06
1239,28
1173,13
1050,22
753,14
696,36

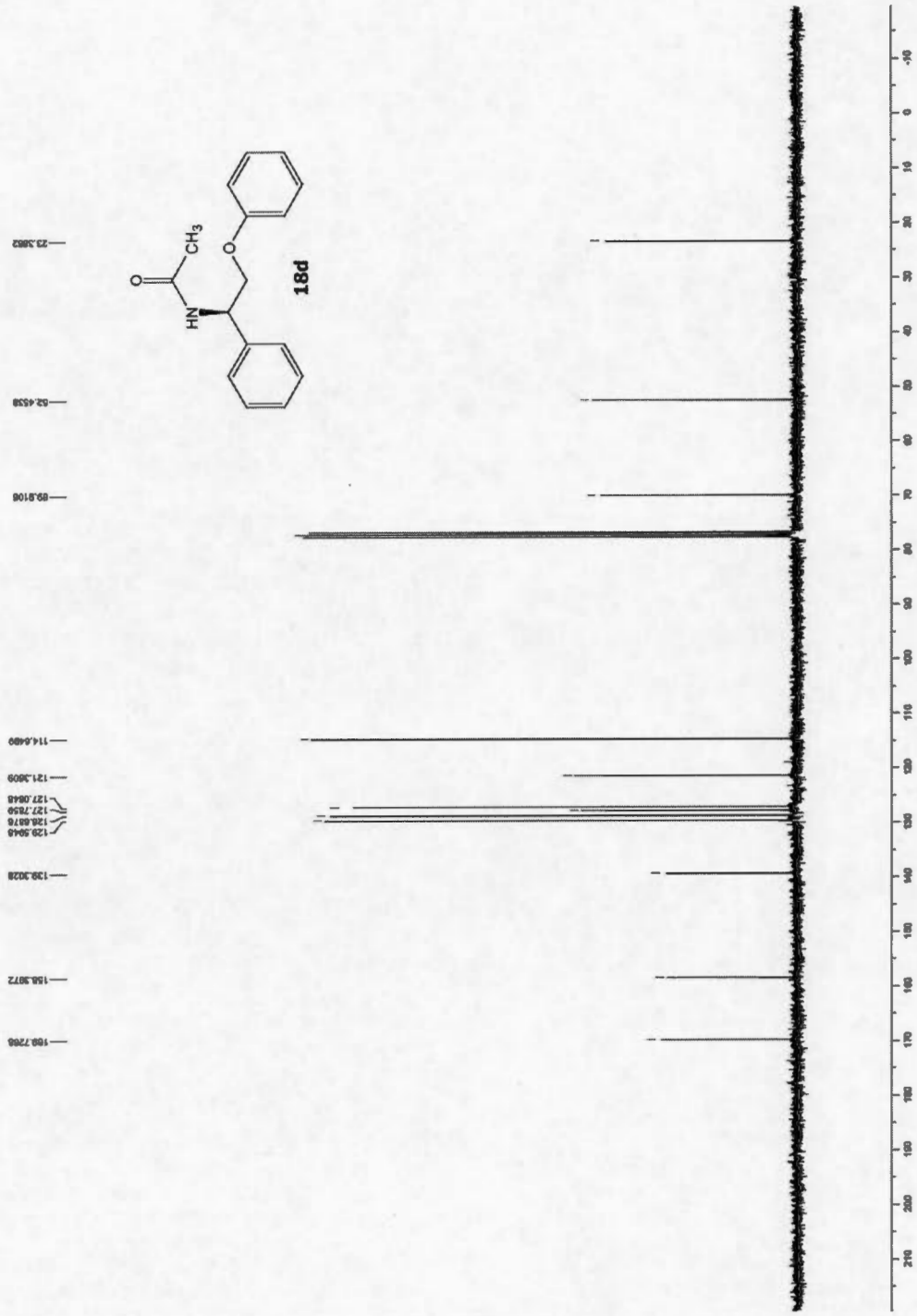

CH3
O
S
O
HN
O
18c


21.8097
87.0530
70.3618
114.8404
121.8322
127.2885
128.0805
128.3530
128.4278
128.8431
137.1633
137.4450
143.8287
157.7986
18c

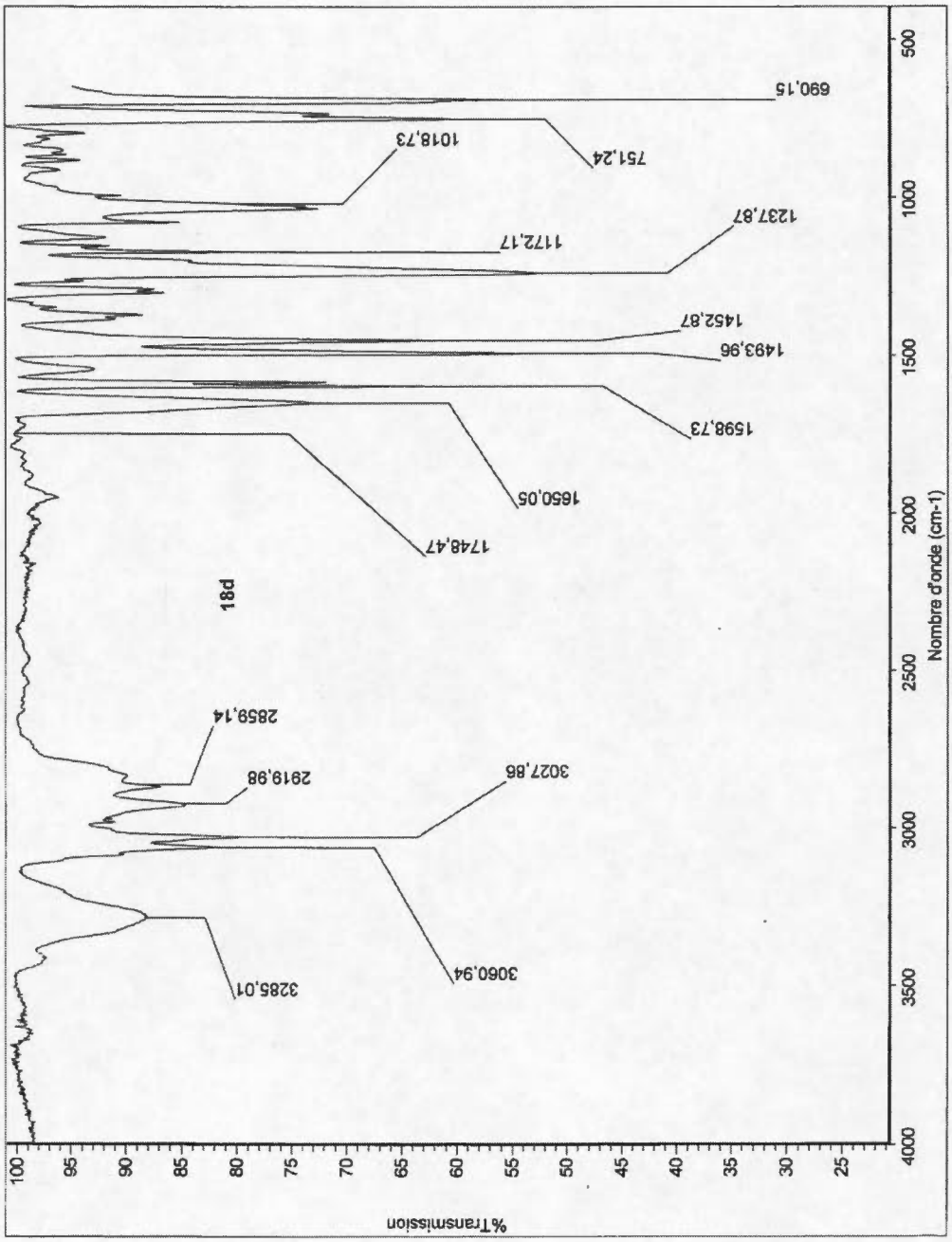

F1 [ppm]
F2 [ppm]
18c
CH3
HN
O
S
O
O
cosy CDCl3 C:\Bruker\TOPSPIN dagoon

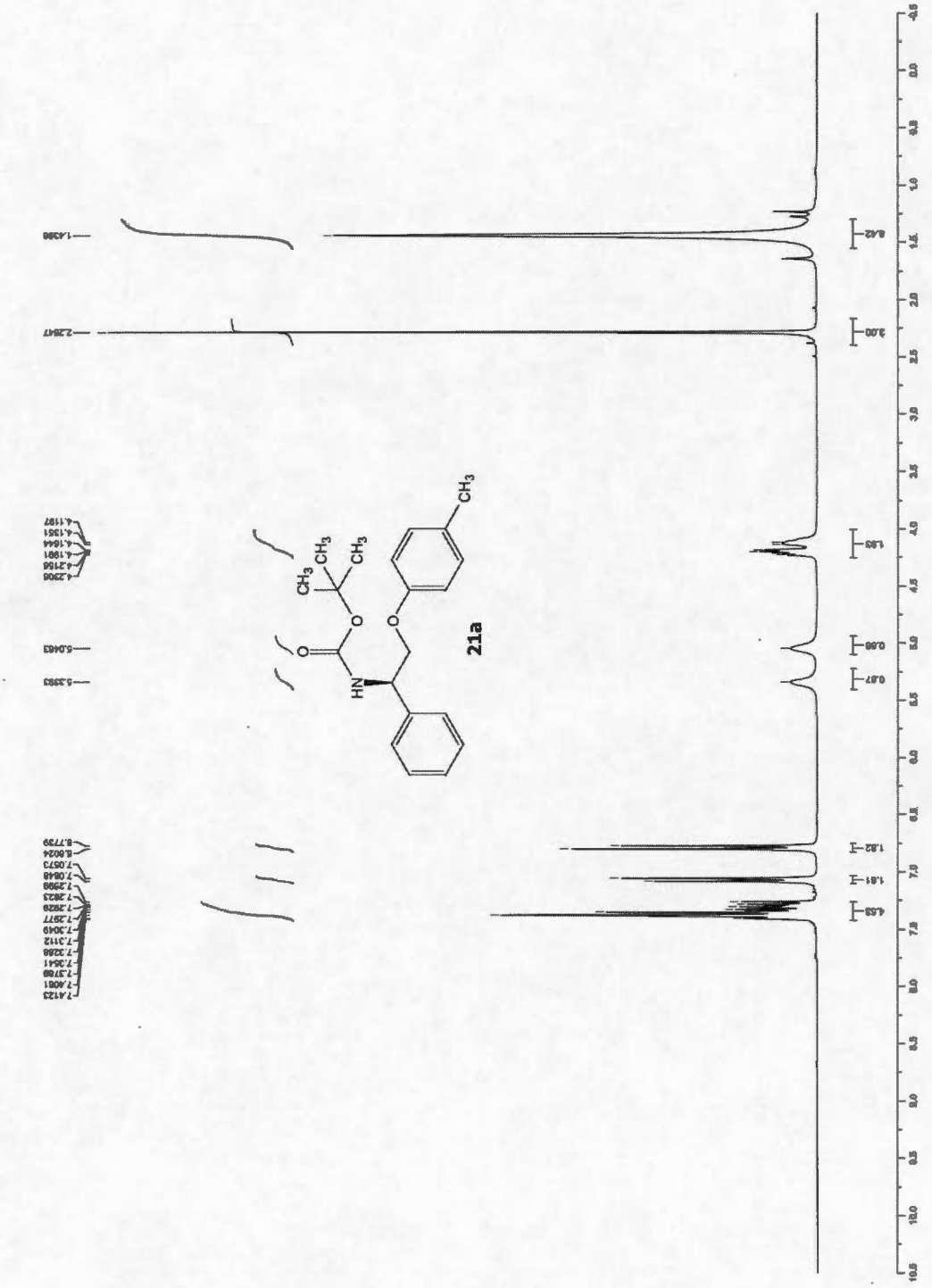

%Transmission
Nombre d'onde (cm-1)
18c
3305,33
2982,89
2925,31
1740,30
1598,27
1497,38
1372,68
1088,63
1044,09
1158,54
753,57
697,98
690,92
670,88

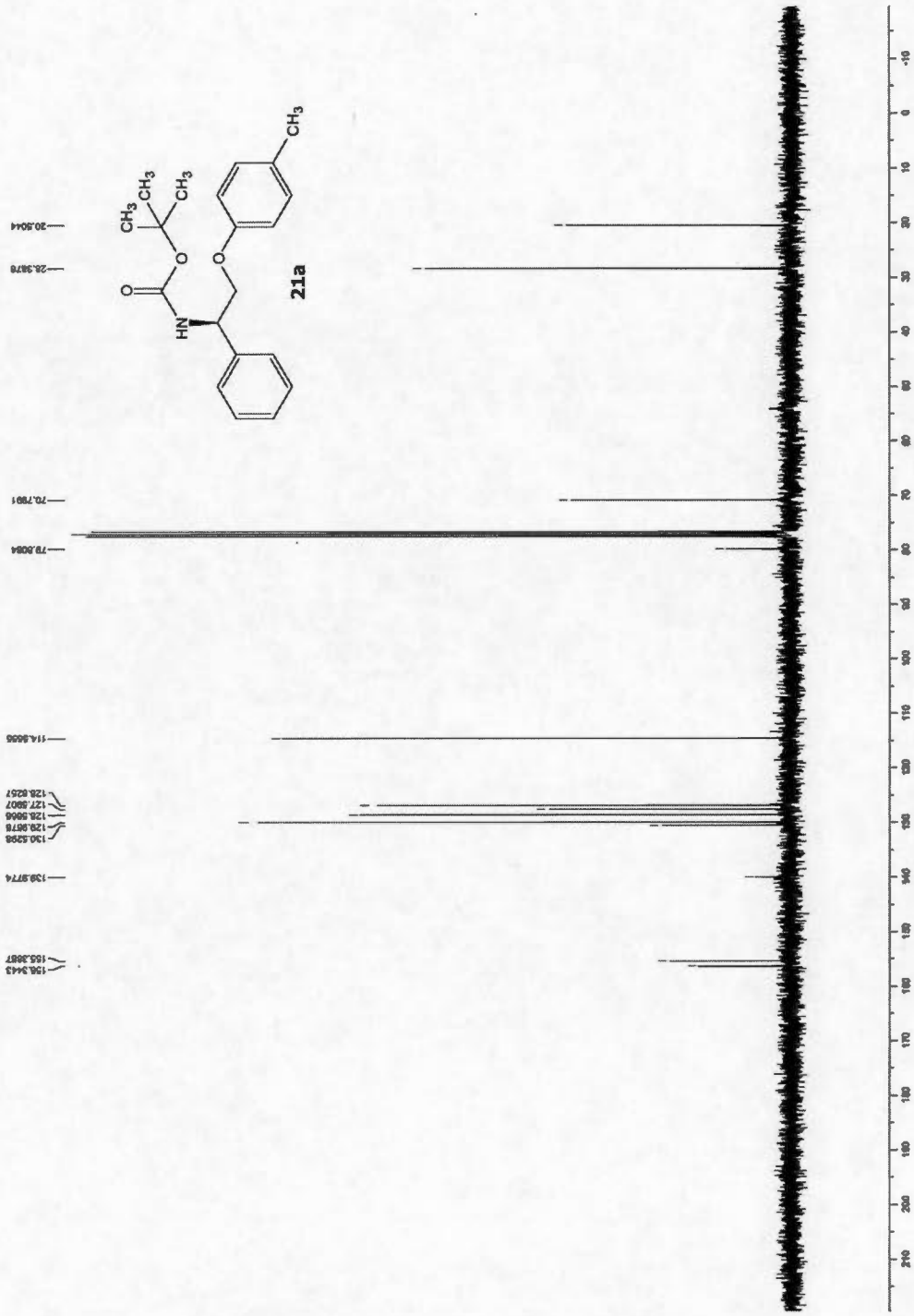

18d
CH3
O
HN
O

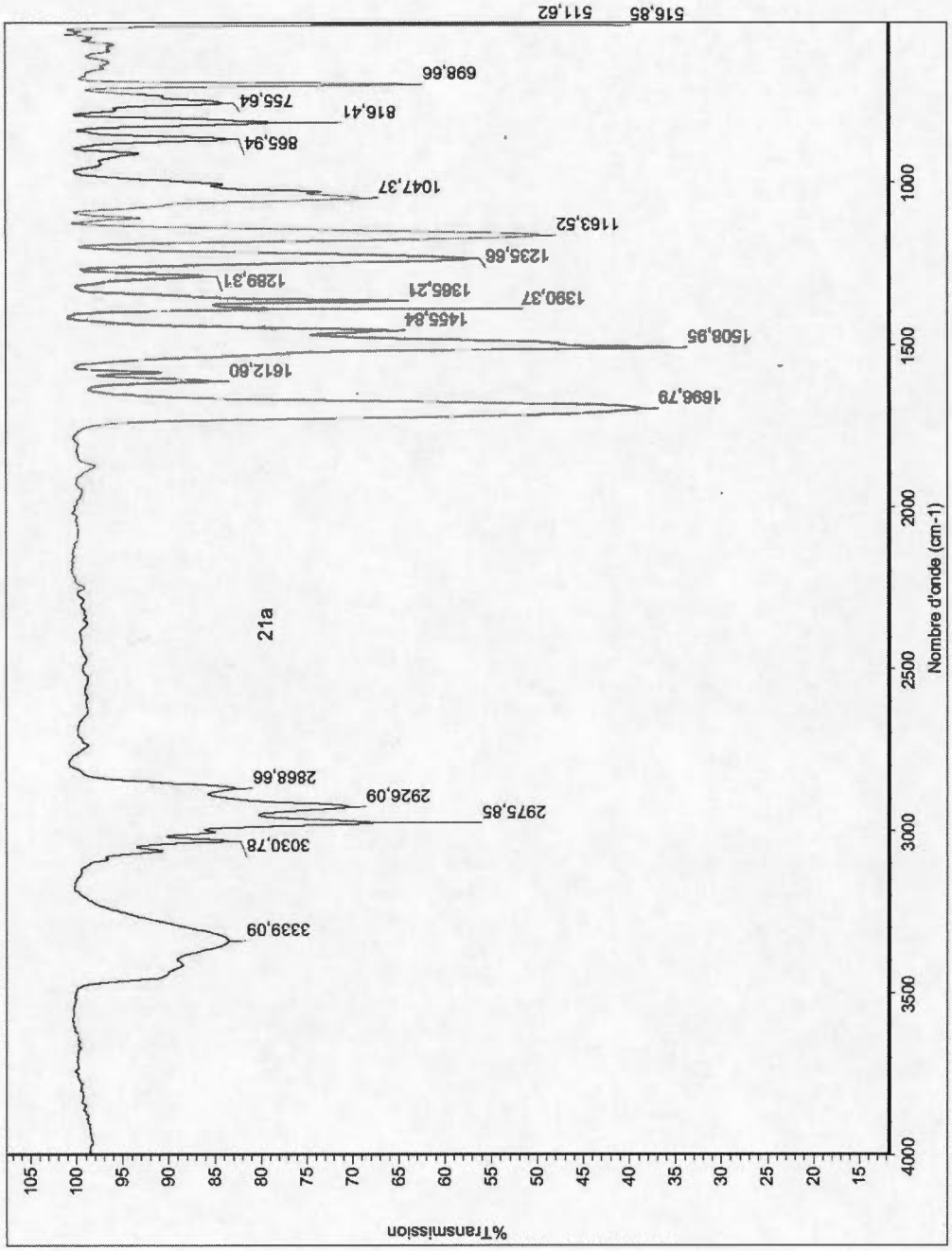

18d
23.3862
52.4558
69.8106
114.6489
121.3609
127.0648
127.7859
128.6878
129.5048
139.3028
158.3872
168.7266

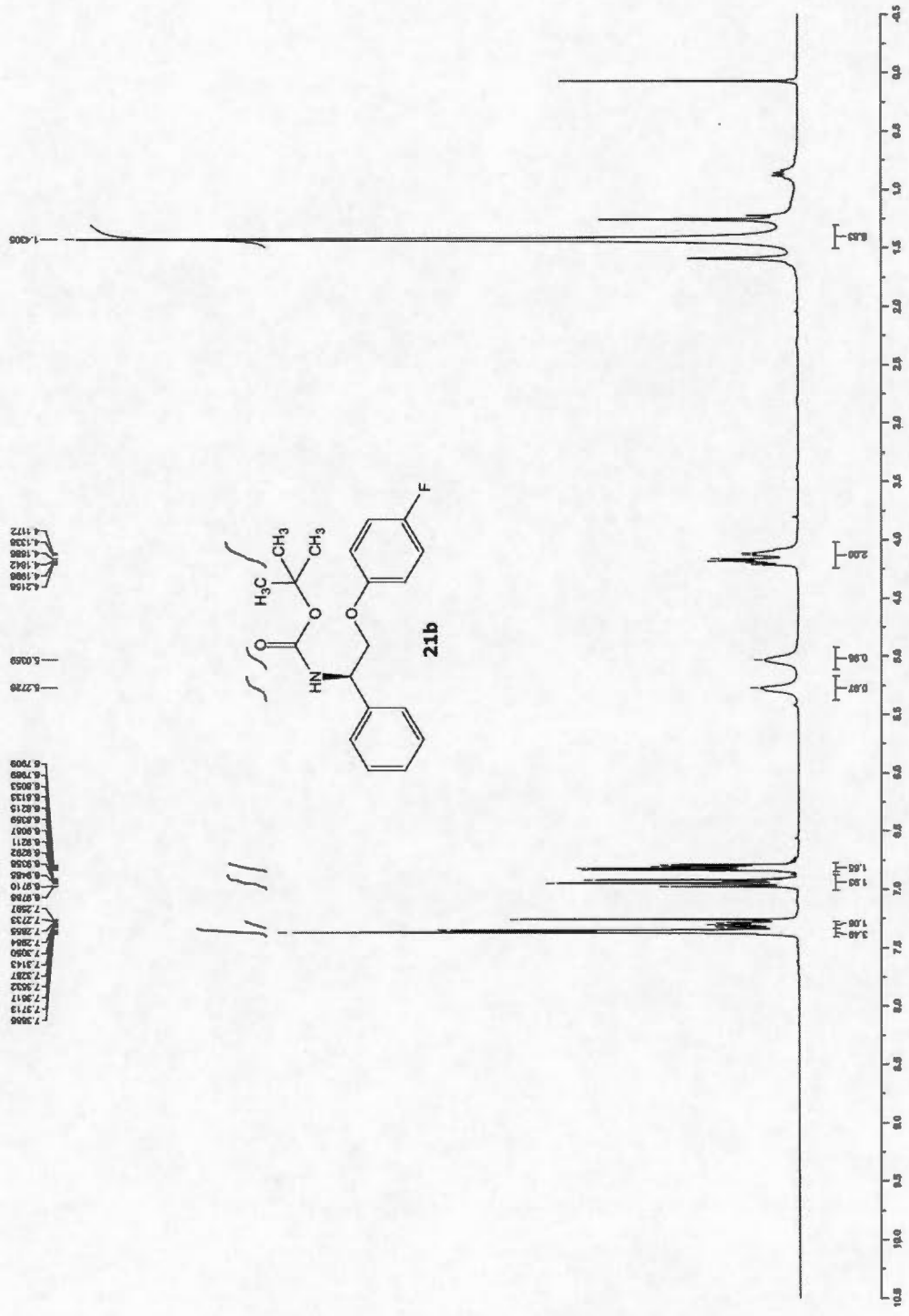

F1 [ppm]
F2 [ppm]
2
4
6
8
HN
O
CH3
O
18d
cosy CDCl3 C:\Bruker\TOPSPIN Gagnon

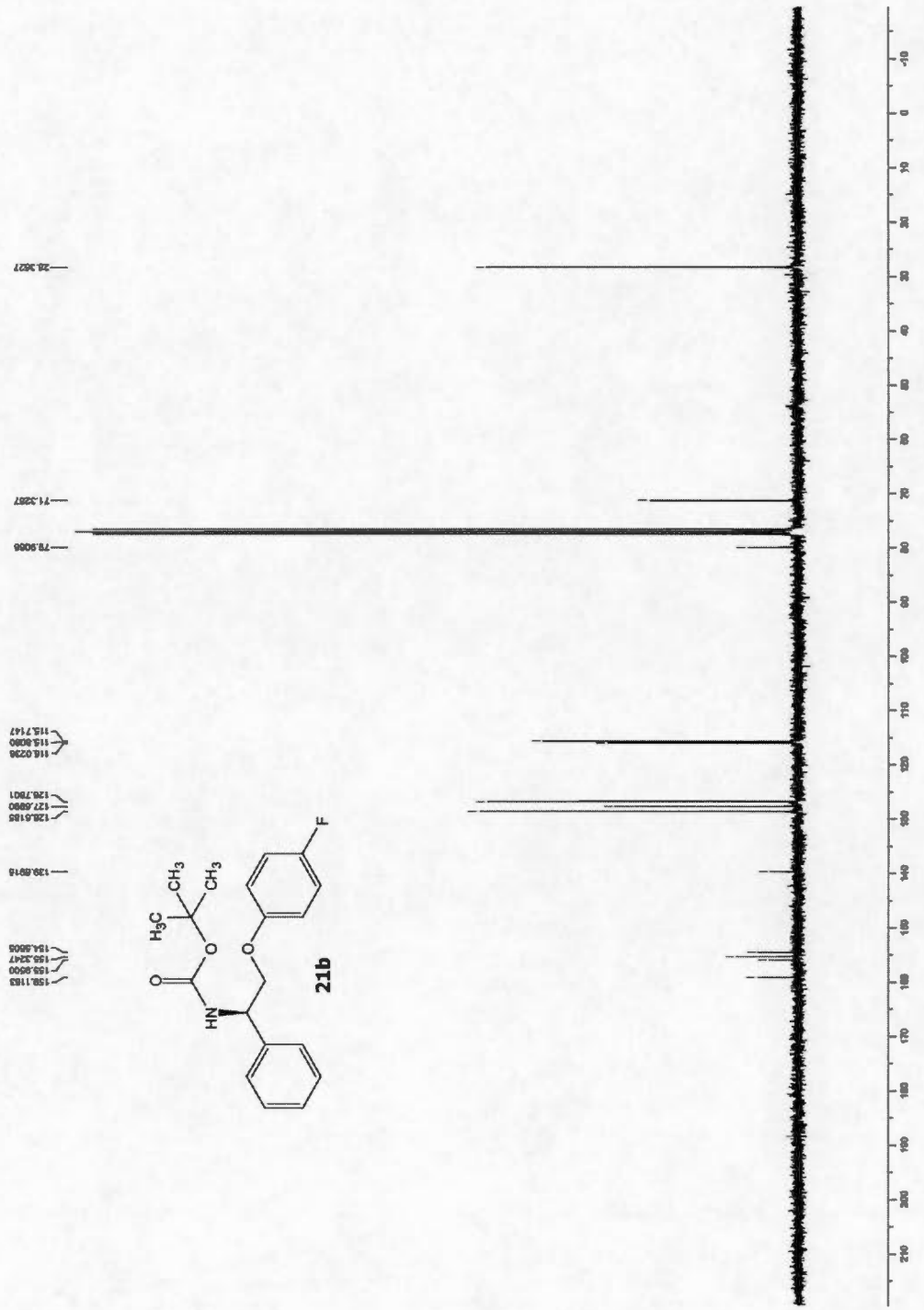

%Transmission
Nombre d'onde (cm-1)
18d
3285,01
3060,94
3027,86
2919,98
2859,14
1748,47
1650,05
1598,73
1493,96
1452,87
1237,87
1172,17
1018,73
751,24
690,15

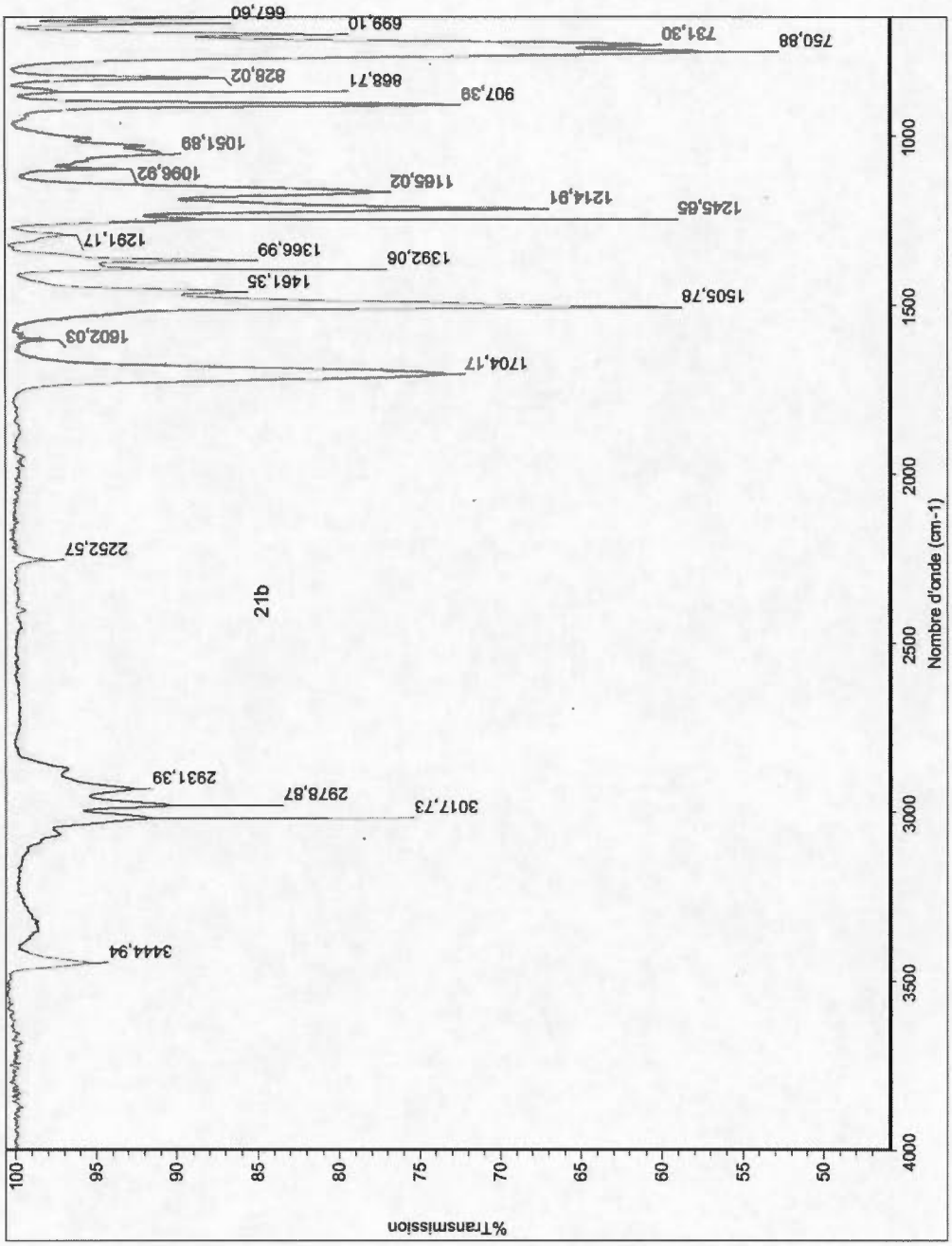

21a

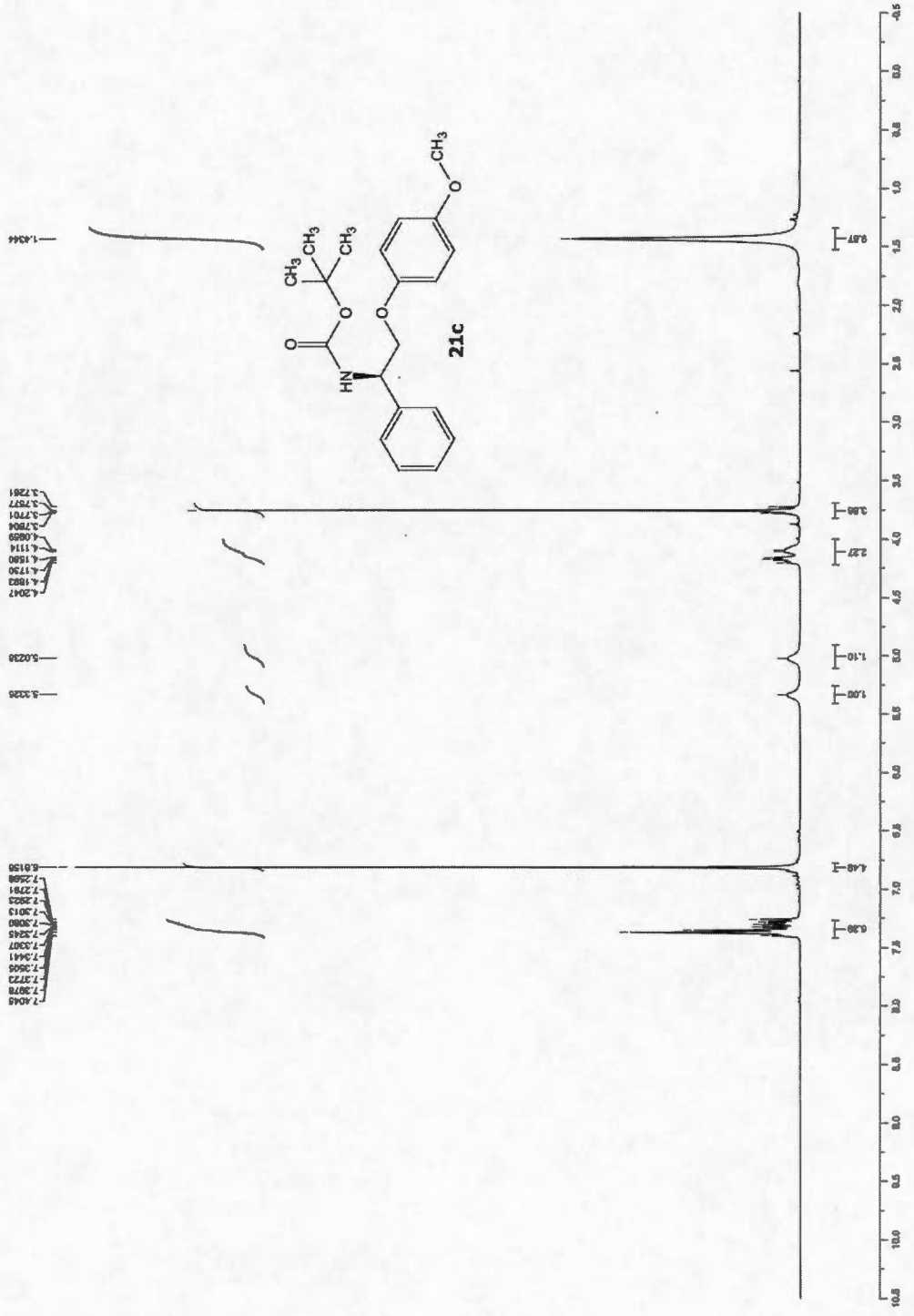

CH3
CH3
CH3
O
O
O
HN
21a
20.9044
28.3878
70.7981
78.8084
114.8656
128.8257
127.8907
128.8966
129.8678
130.5298
139.8774
156.3443
156.3887

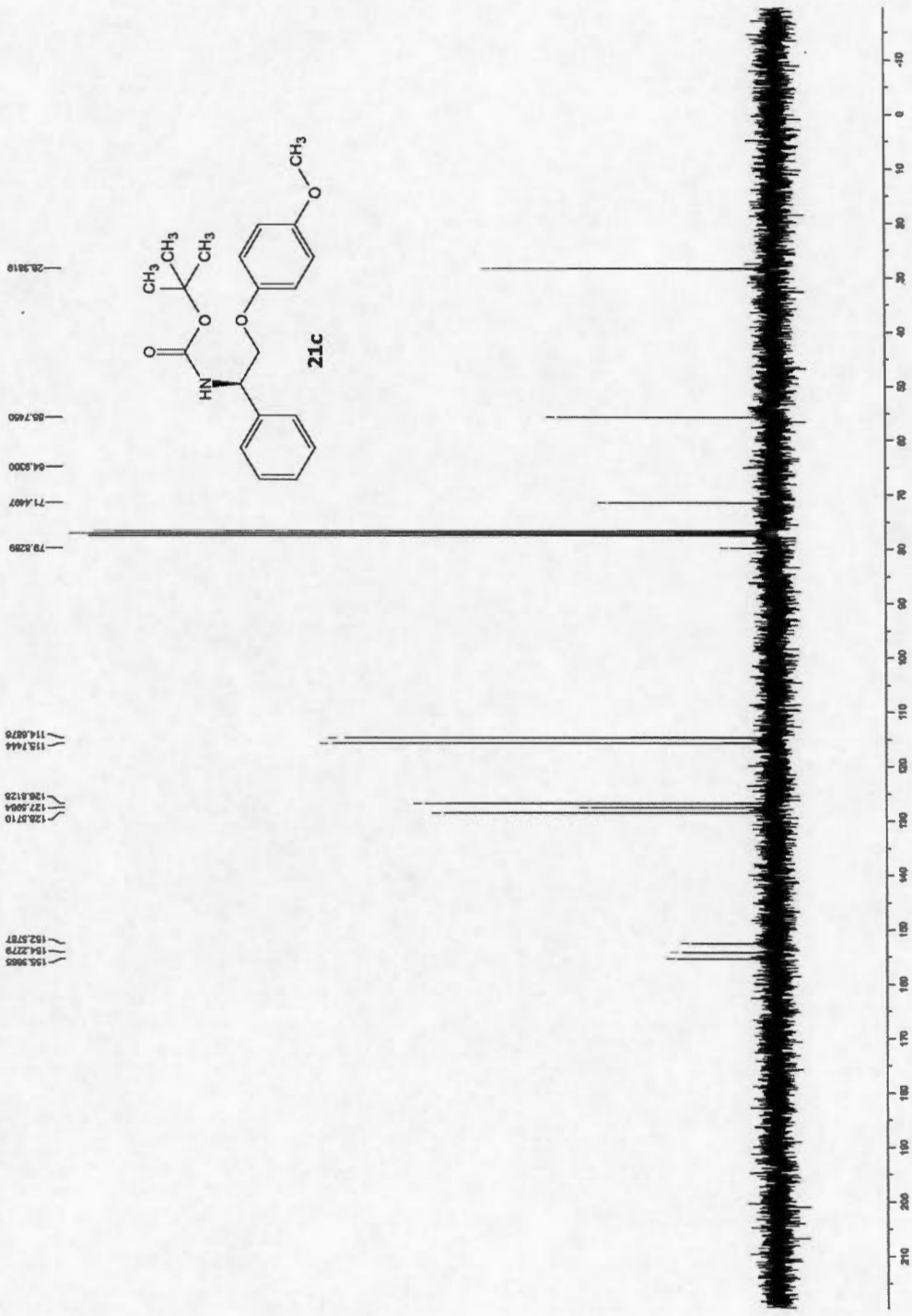

%Transmission
Nombre d'onde (cm-1)
21a
516,85
511,62
698,66
816,41
755,64
865,94
1047,37
1163,52
1235,66
1289,31
1385,21
1390,37
1455,84
1508,95
1612,60
1696,79
2868,66
2926,09
2975,85
3030,78
3339,09

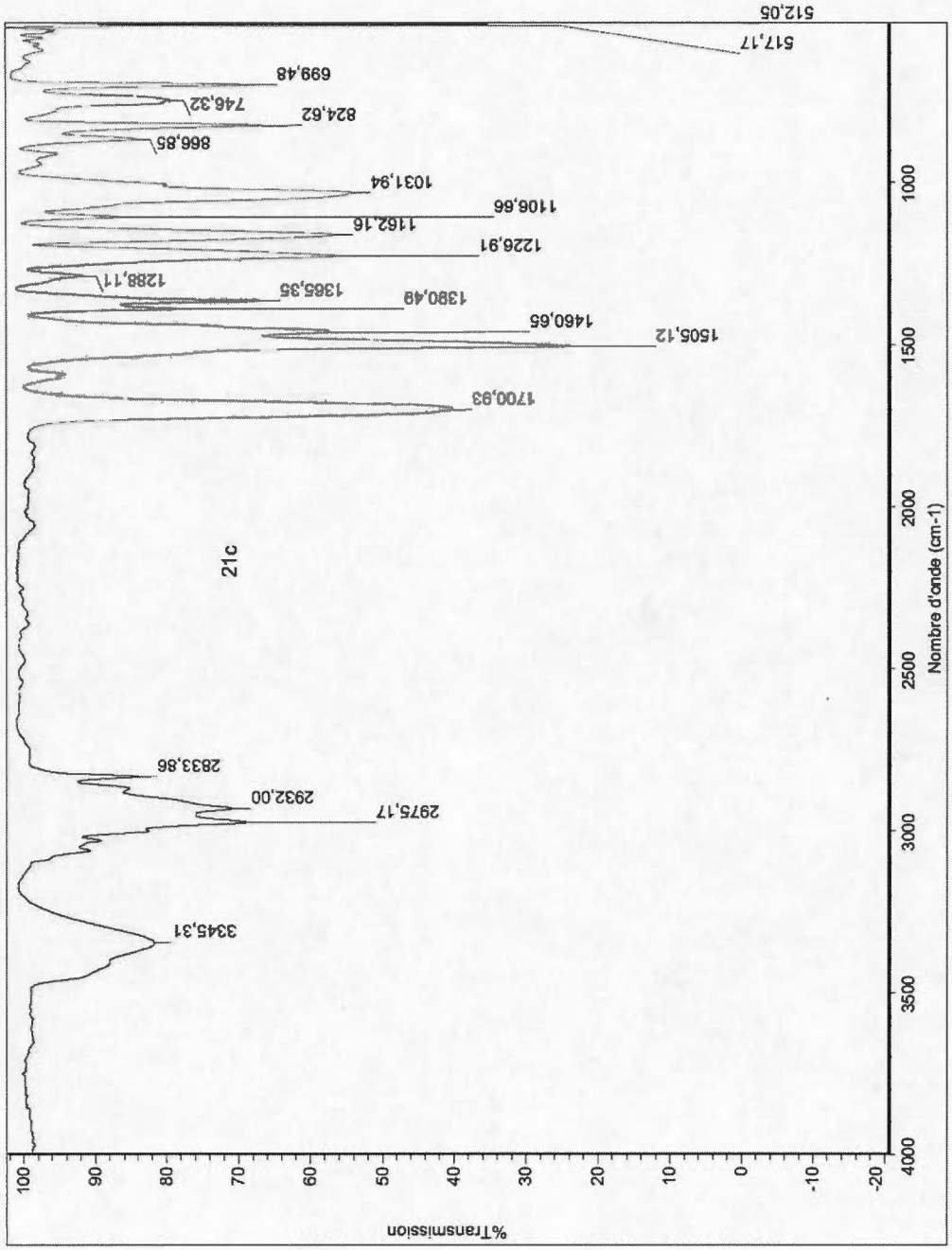

21b
F
O
O
HN
CH3
CH3
H3C

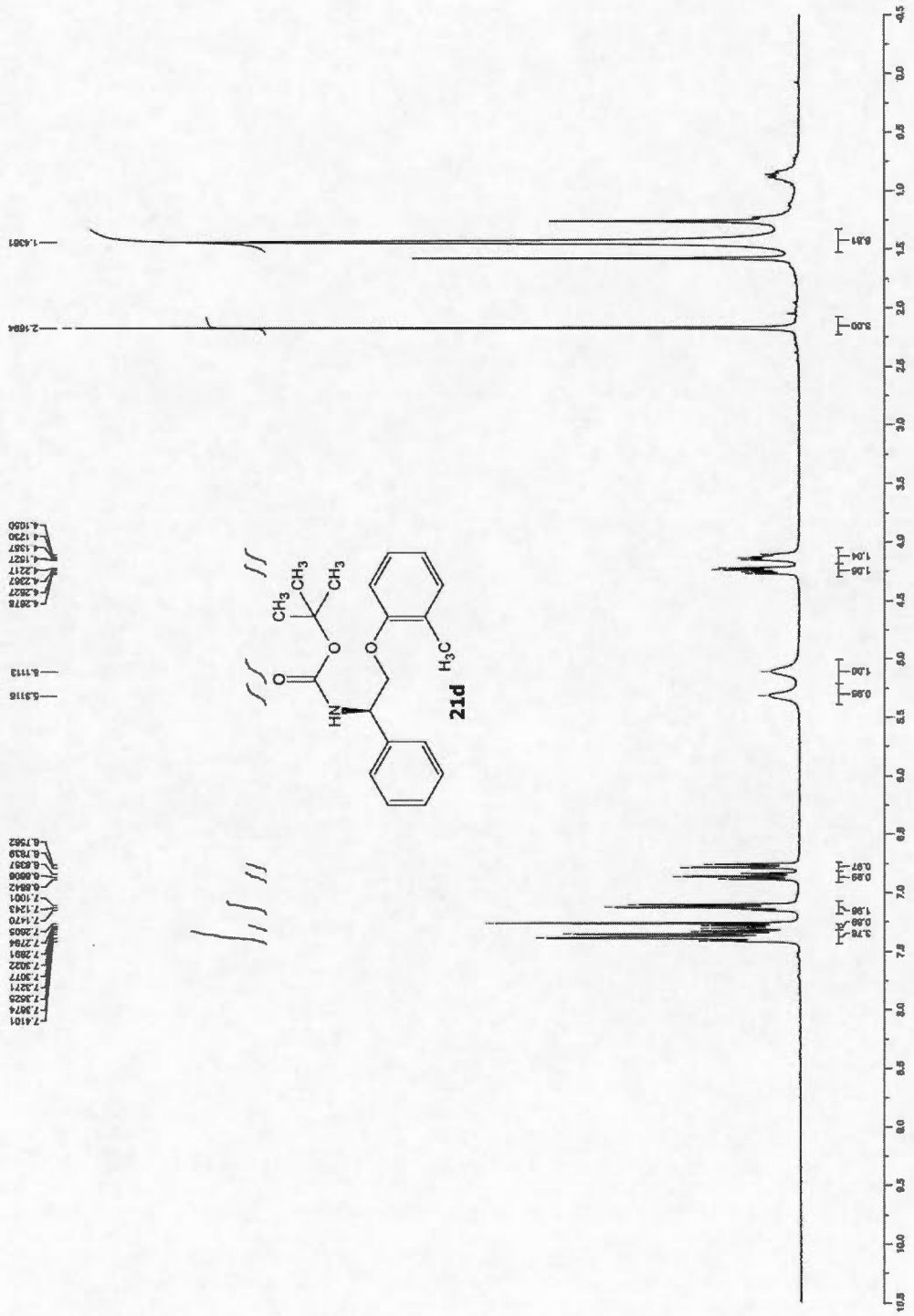

28.3627
71.3287
79.5066
116.0236
116.3080
116.7147
128.6185
127.6980
126.7801
139.8916
158.1183
155.9500
155.3247
154.8005
F
O
O
HN
CH3
CH3
H3C
21b

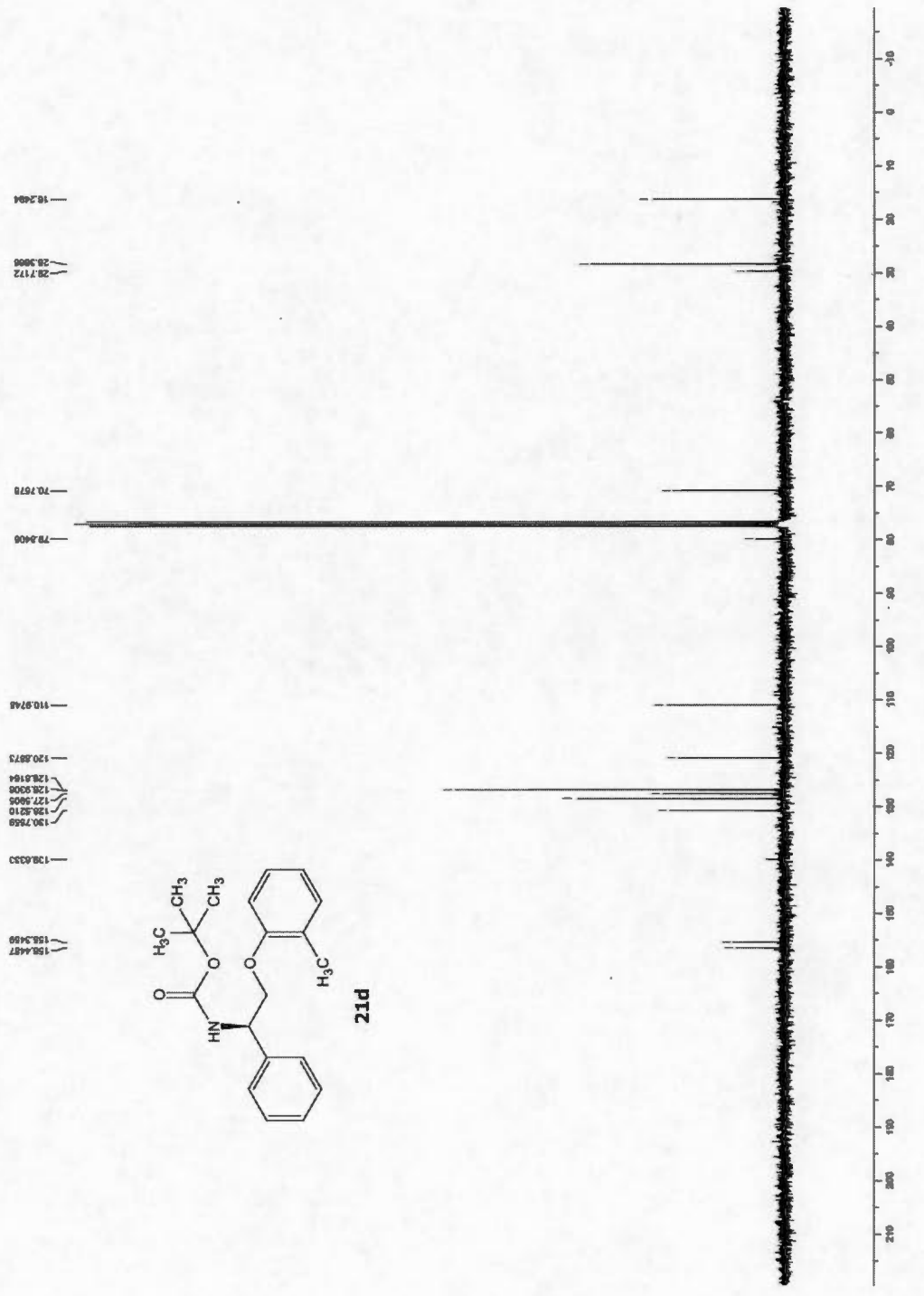

%Transmission
Nombre d'onde (cm-1)
21b
3444,94
3017,73
2978,87
2931,39
2252,57
1704,17
1602,03
1505,78
1461,35
1392,06
1366,99
1291,17
1245,85
1214,91
1165,02
1096,92
1051,89
907,38
868,71
828,02
750,88
731,30
699,10
667,60


21c

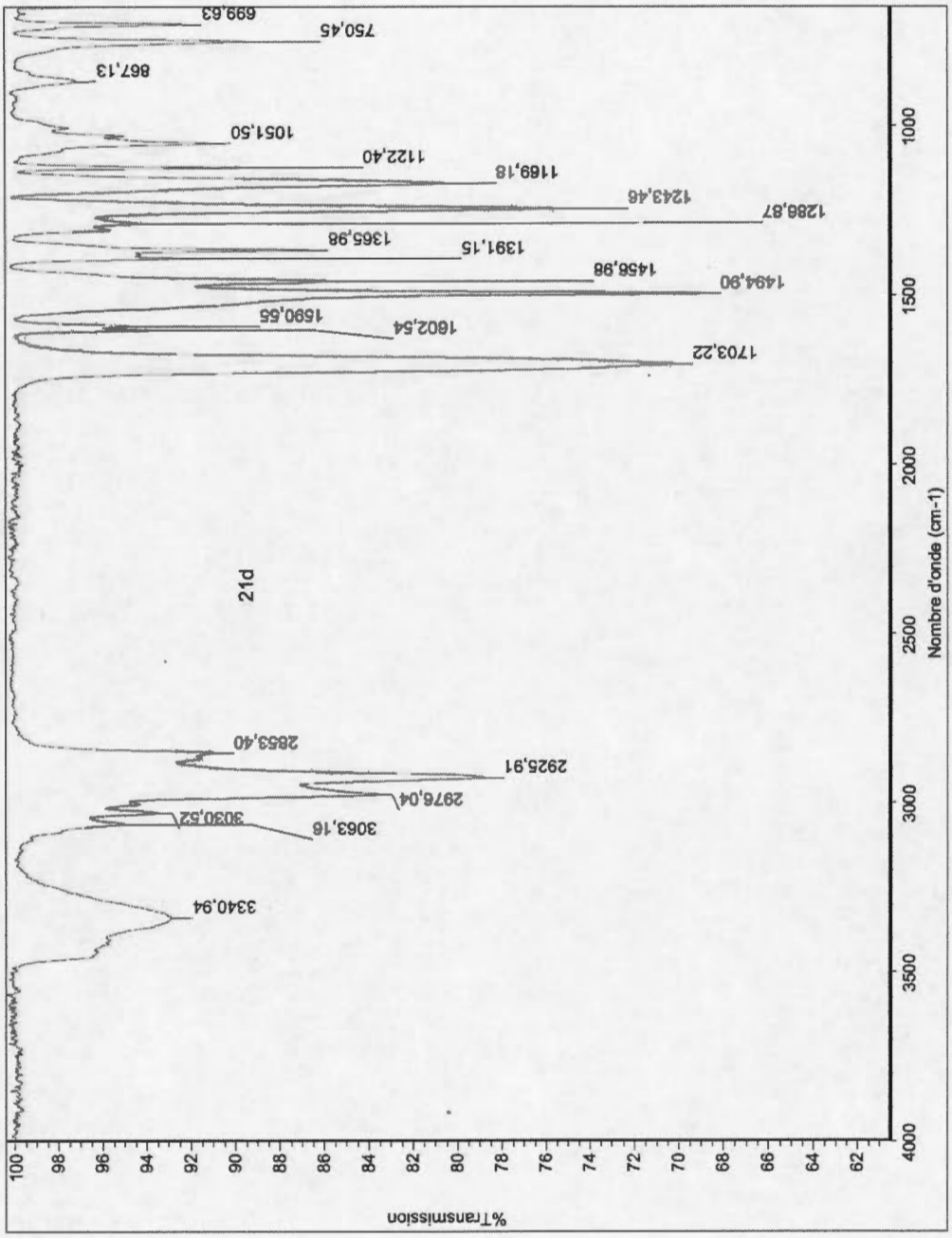

21c
28.3818
55.7450
64.8300
71.4407
79.8289
114.6870
115.7444
128.5710
127.5804
128.8128
152.5787
154.2279
156.3665

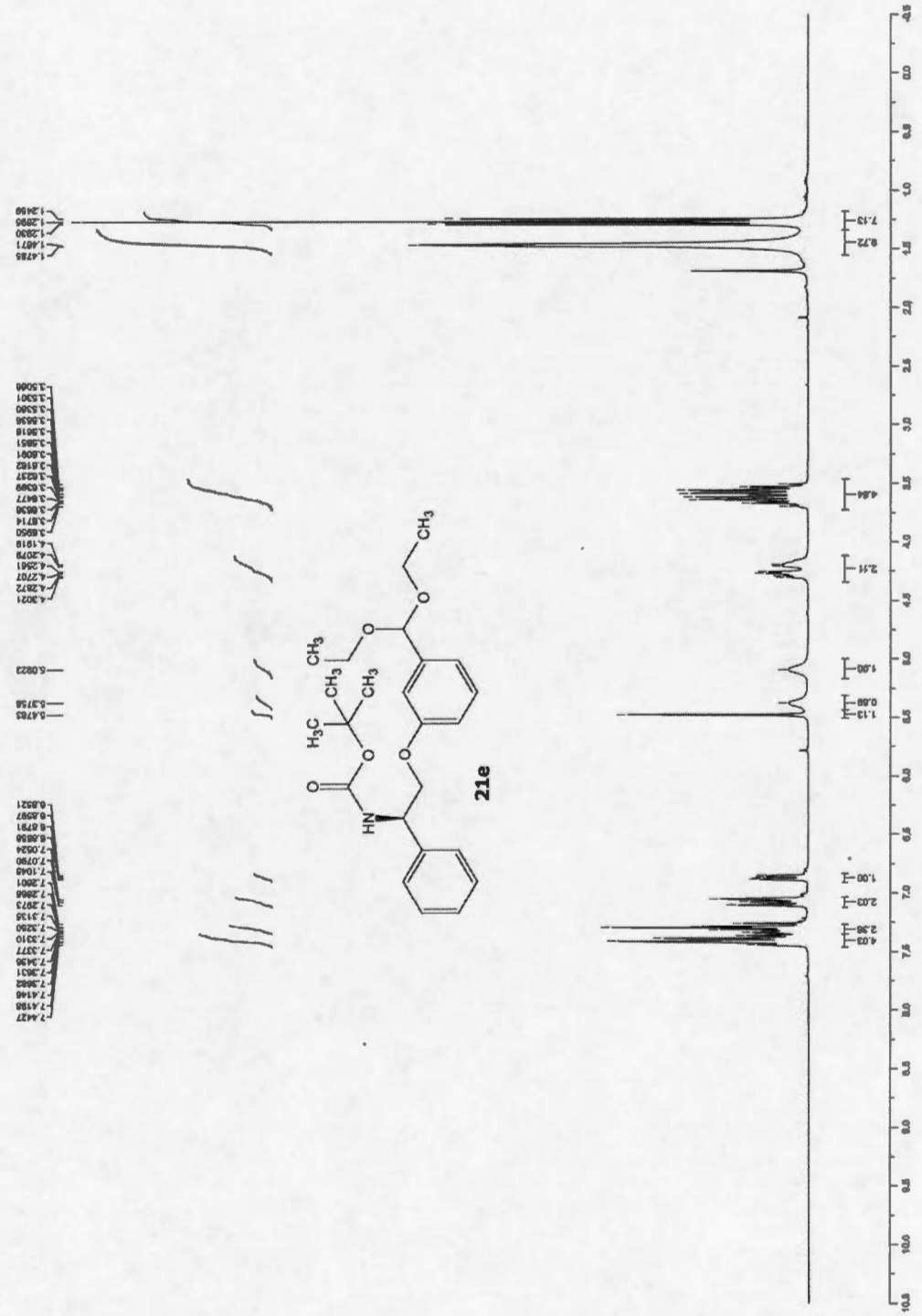

%Transmission
100
90
80
70
60
50
40
30
20
10
0
-10
-20
4000
3500
3000
2500
2000
1500
1000
Nombre d'onde (cm-1)
21c
3345,31
2975,17
2932,00
2833,86
1700,93
1505,12
1460,65
1380,49
1365,35
1288,11
1226,91
1162,16
1106,66
1031,94
866,85
824,62
746,32
699,48
517,17
512,05

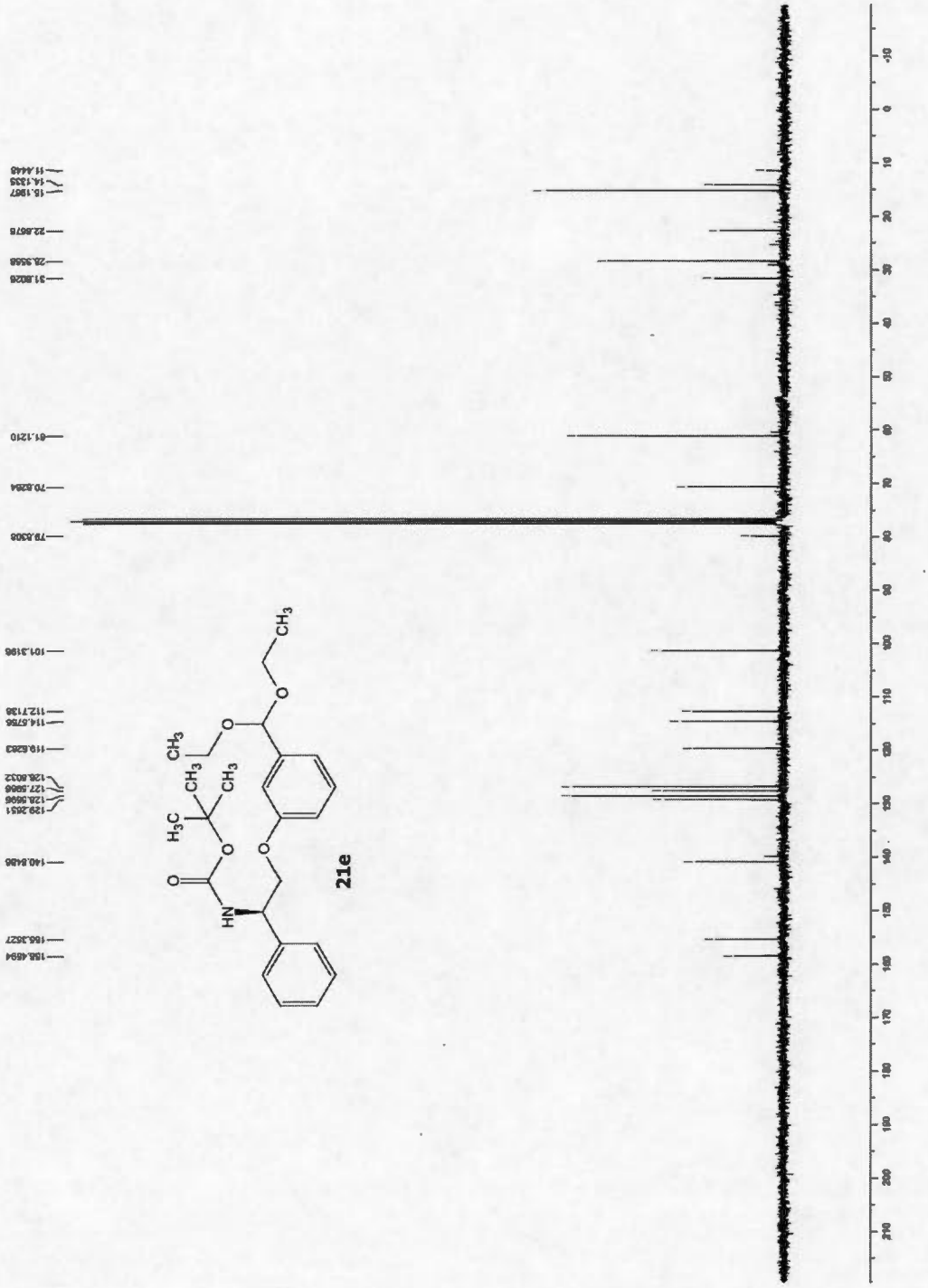

21d

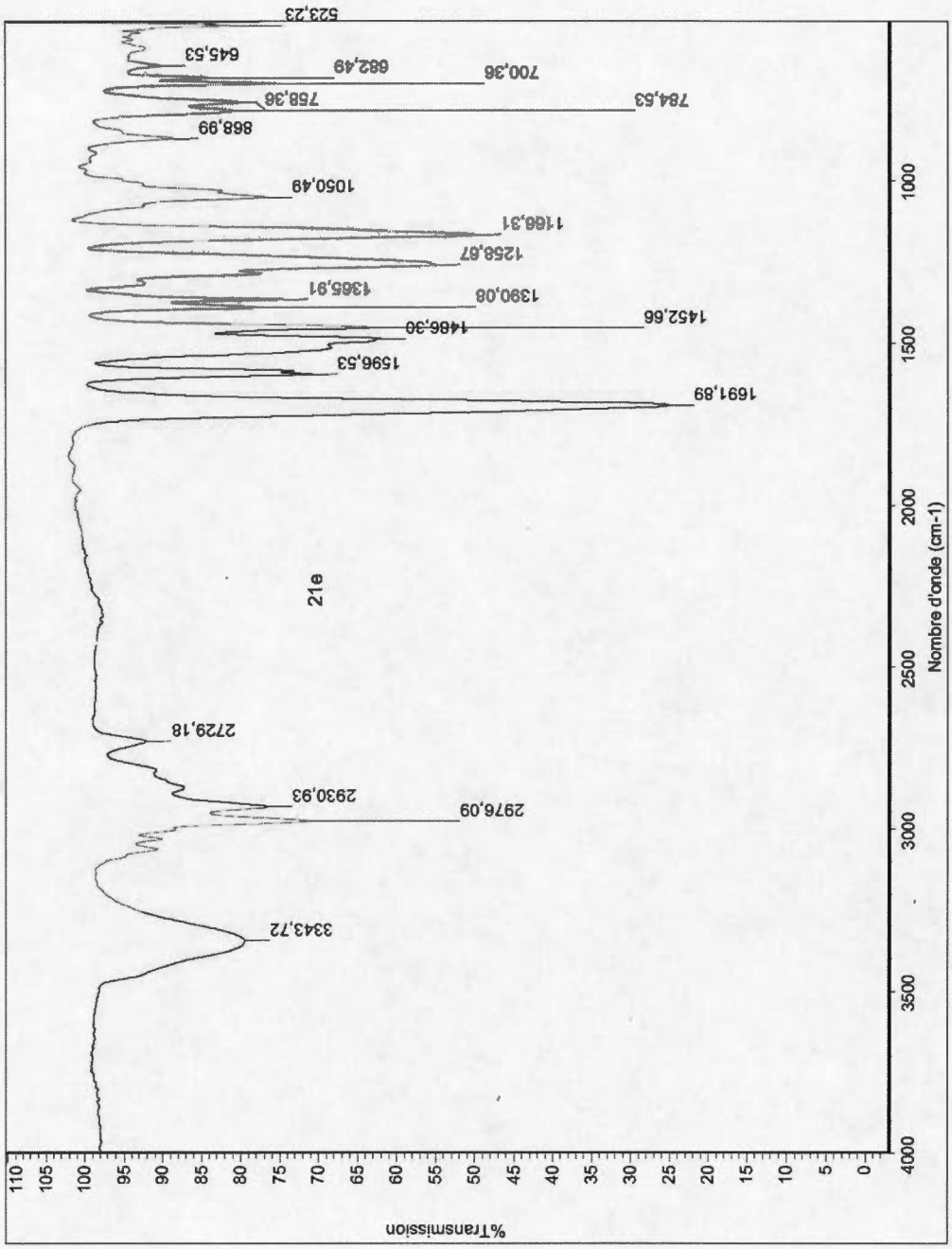

18.2484
28.3866
28.7172
70.7578
78.9408
110.9748
120.8873
128.8164
128.9306
127.3805
130.3210
130.7569
138.6333
158.3469
158.4487
H3C
CH3
CH3
O
O
O
HN
H3C

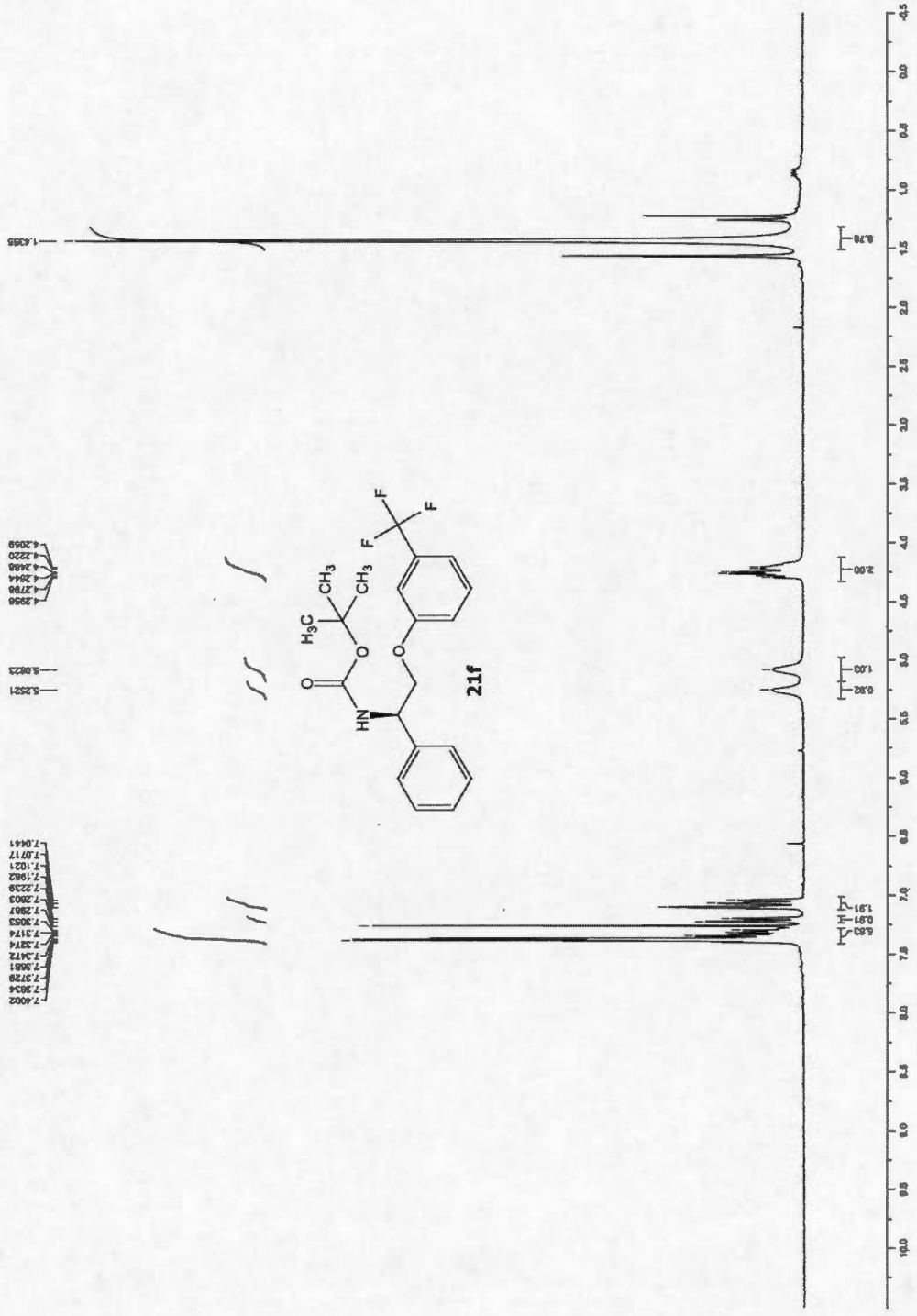
21d

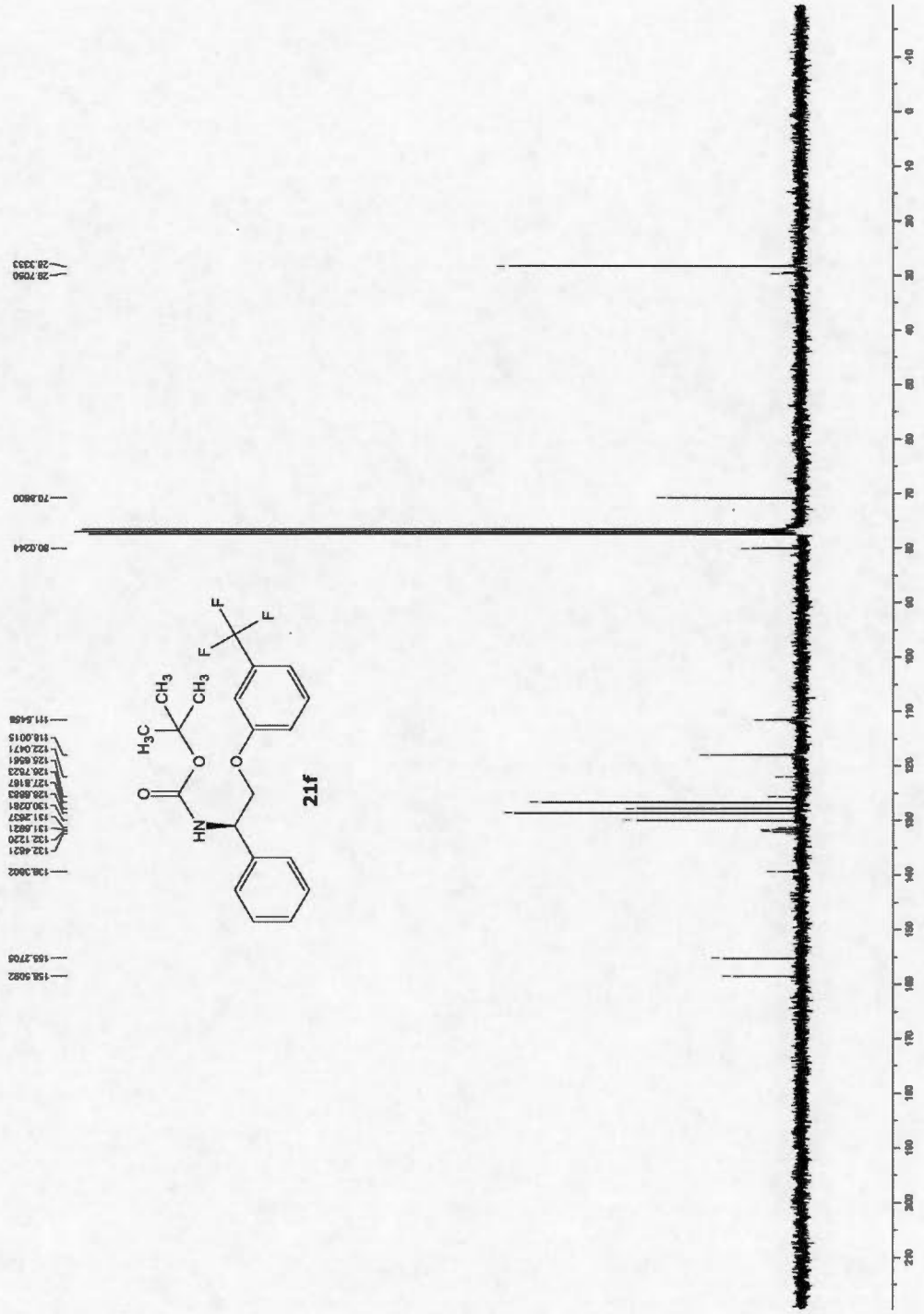

%Transmission
Nombre d'onde (cm-1)
21d
3340,94
3063,16
3030,52
2976,04
2925,91
2853,40
1703,22
1602,54
1590,55
1494,90
1456,88
1391,15
1365,98
1286,87
1243,46
1169,18
1122,40
1051,50
867,13
750,45
699,63

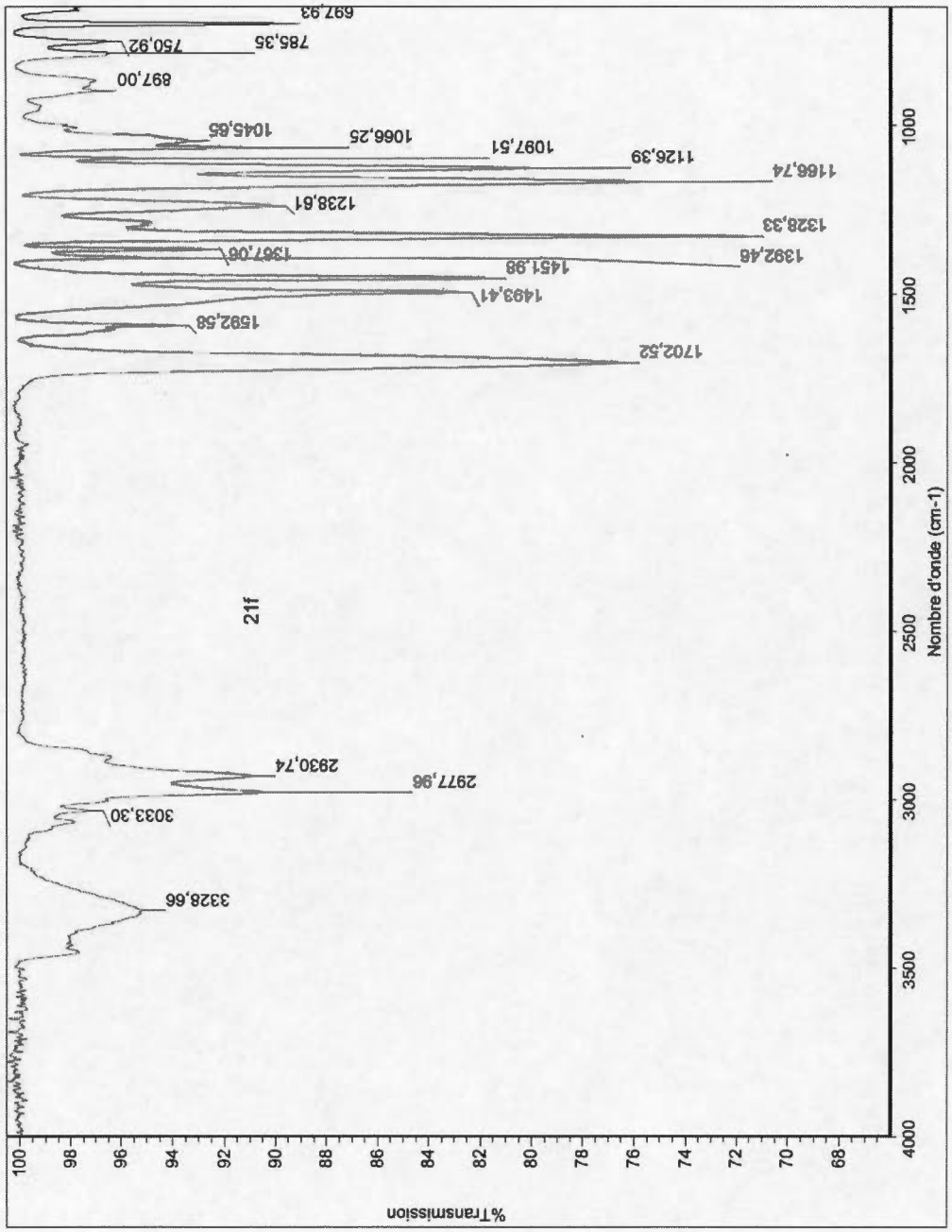

21e

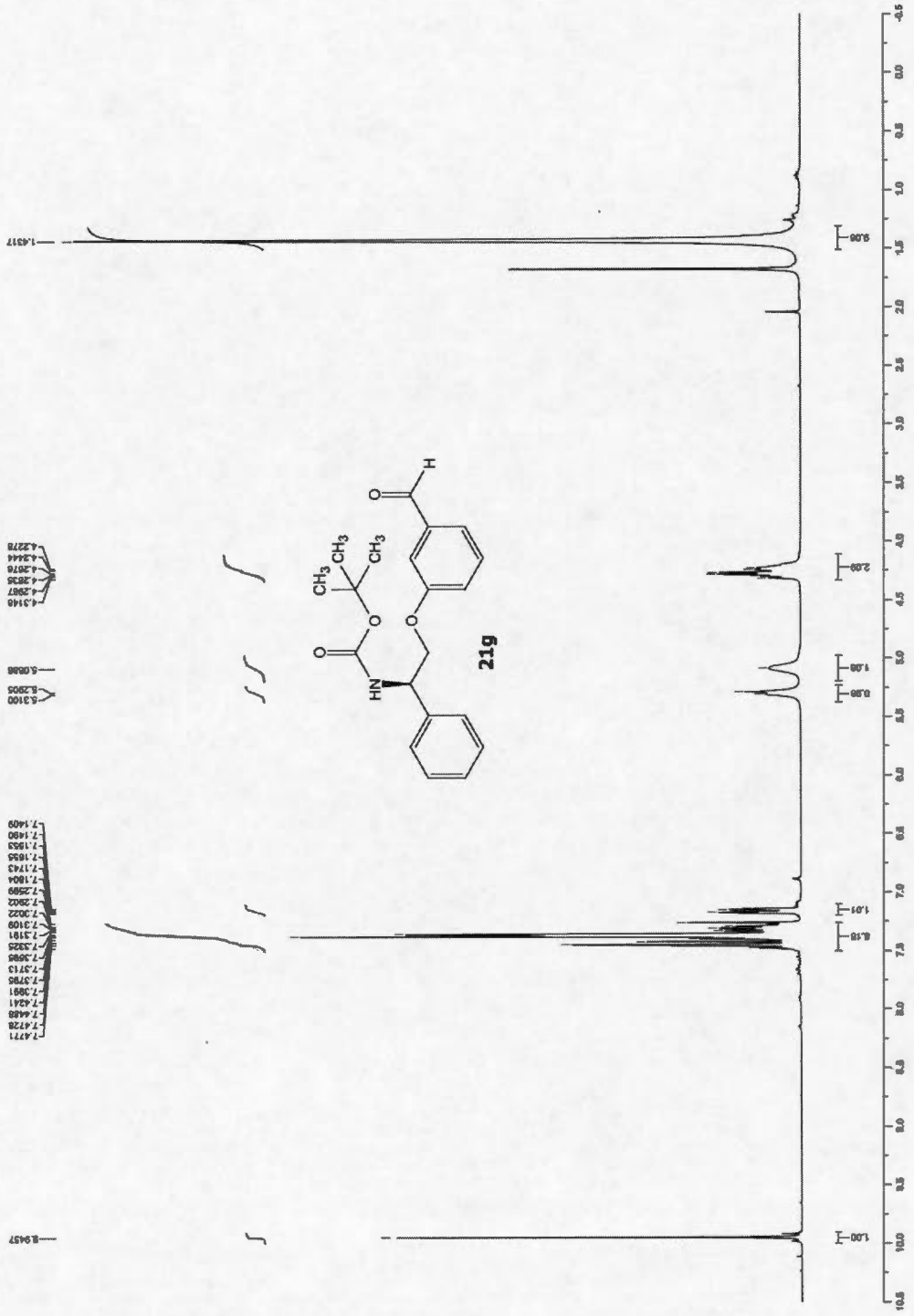

11.4448
14.1335
15.1867
22.8678
28.3568
31.8026
61.1210
70.8284
78.5308
101.3196
112.7136
114.5756
119.6263
128.8032
127.5866
120.9906
129.2651
140.8486
156.3627
158.4694
21e

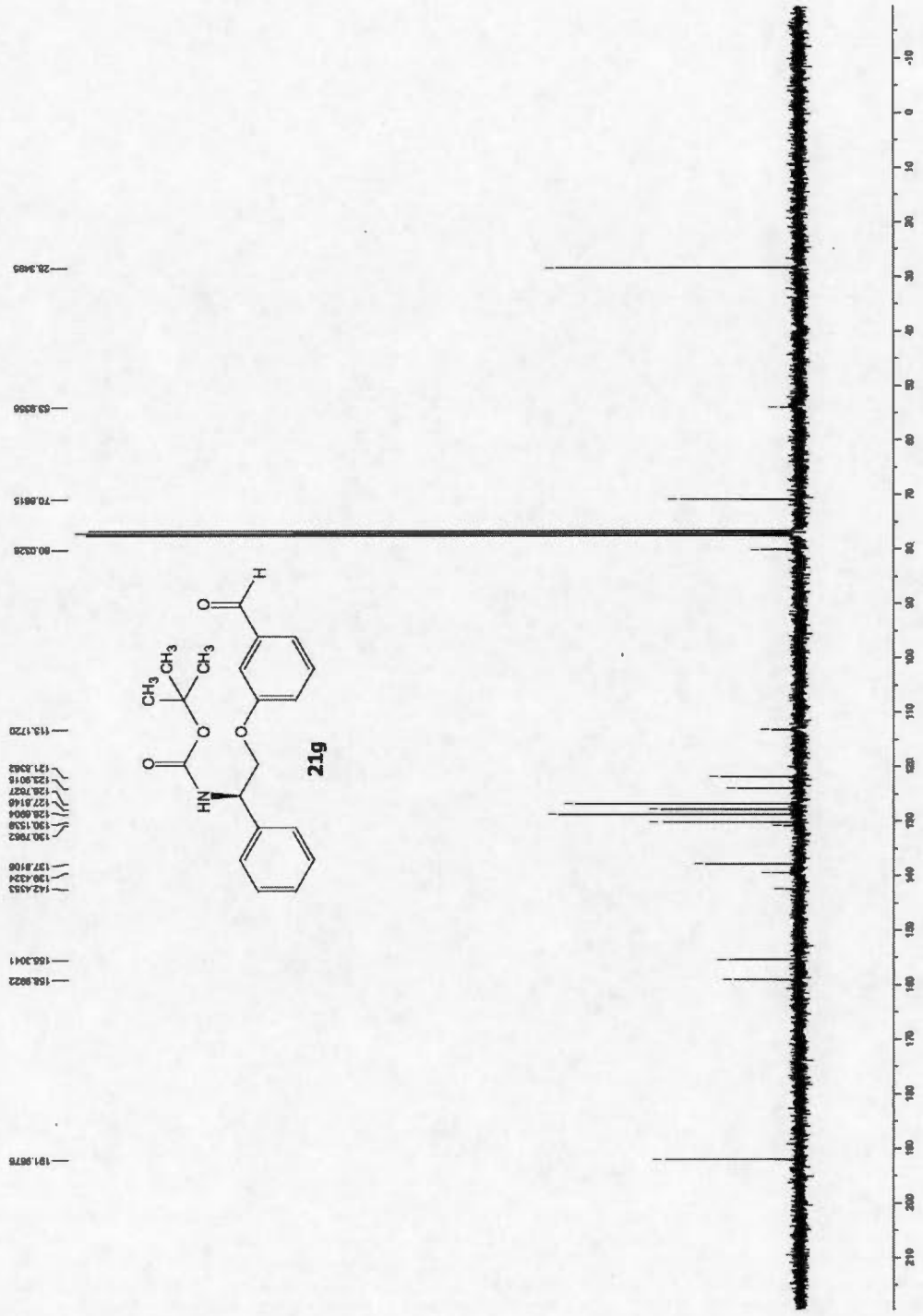

%Transmission
Nombre d'onde (cm-1)
21e
3343,72
2976,09
2930,93
2729,18
1691,89
1596,53
1486,30
1452,66
1390,08
1365,91
1258,87
1166,31
1050,49
868,99
784,53
758,36
700,36
682,49
645,53
523,23

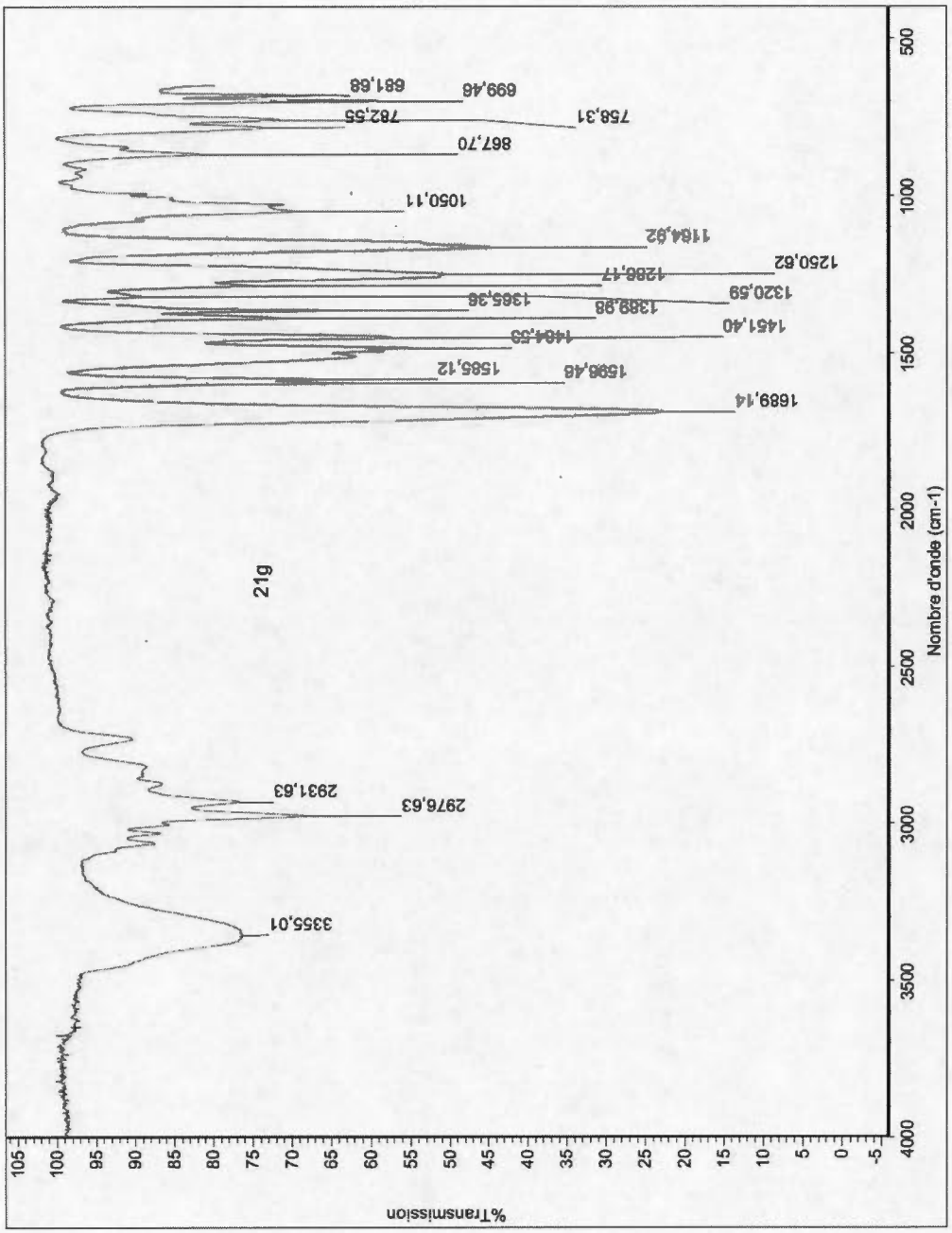

21f

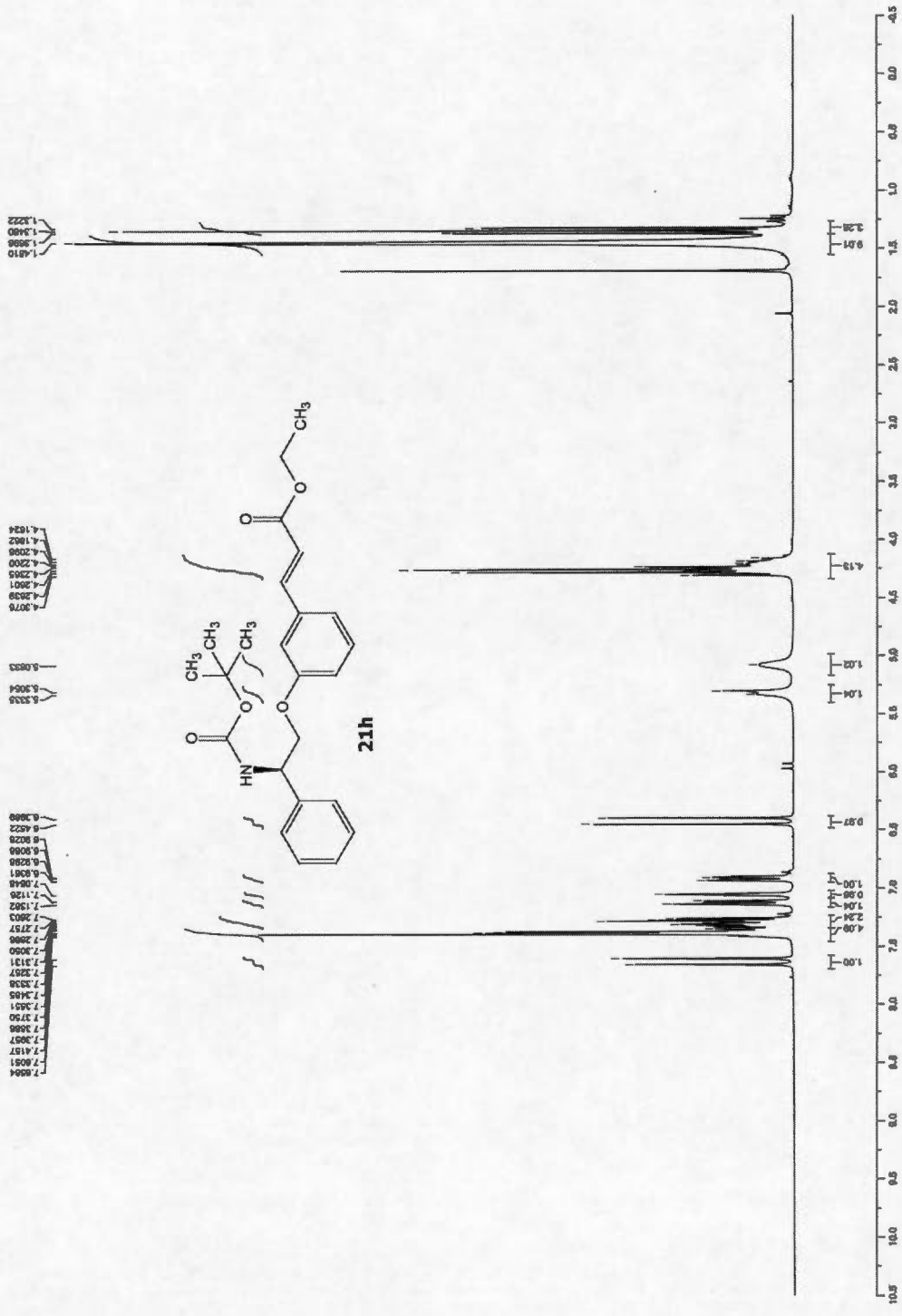

28.7050
28.3353
80.0244
70.8800
111.5468
118.0015
122.0471
125.6561
126.7523
127.8187
128.8653
130.0261
131.3637
131.3821
132.1220
132.4521
138.3802
155.2705
158.5092
21f


%Transmission
Nombre d'onde (cm-1)
21f
3328,66
3033,30
2977,96
2930,74
1702,52
1592,58
1493,41
1451,98
1392,46
1367,06
1328,33
1238,61
1166,74
1126,39
1097,51
1066,25
1045,65
897,00
785,35
750,92
697,93

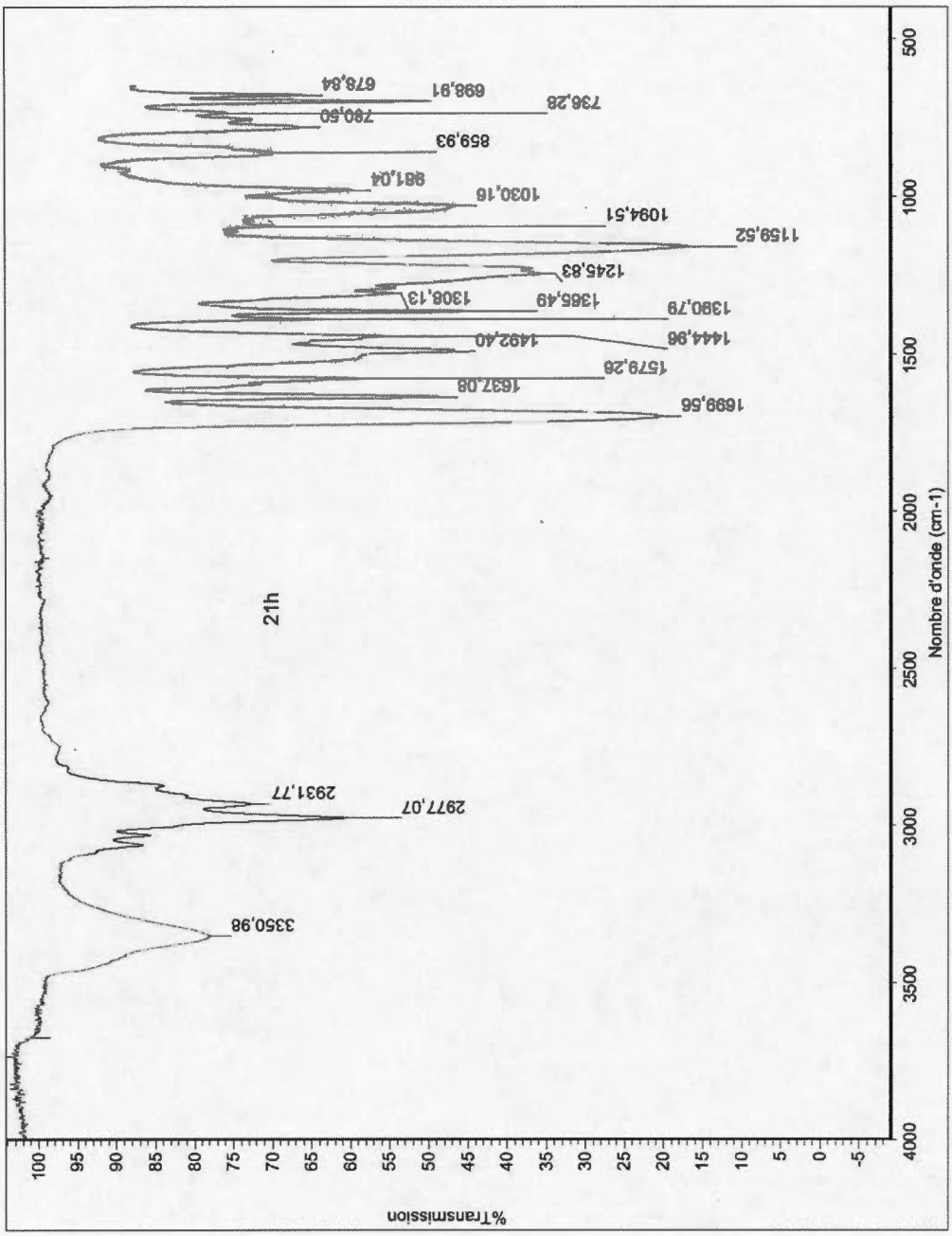

21g

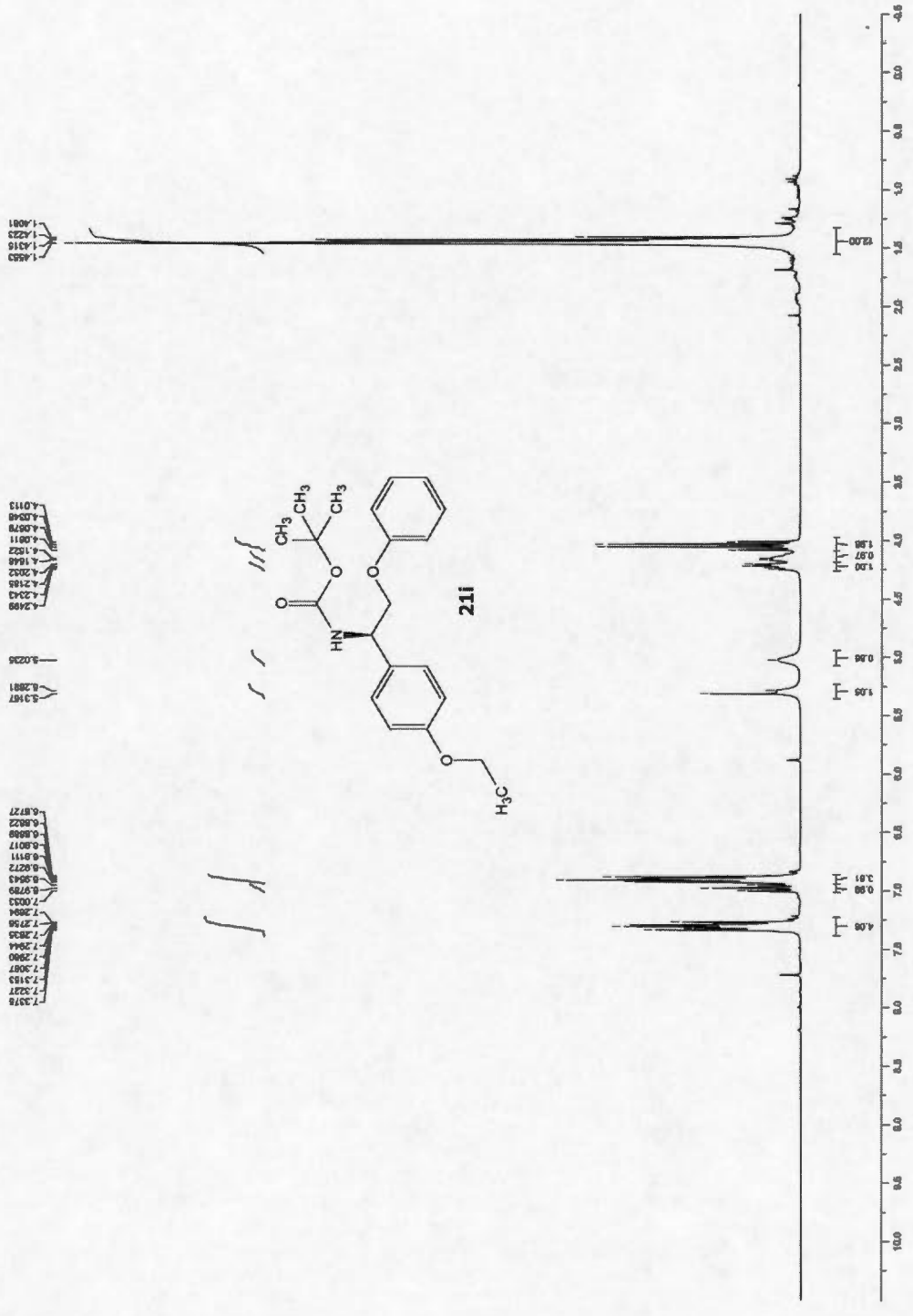

21g

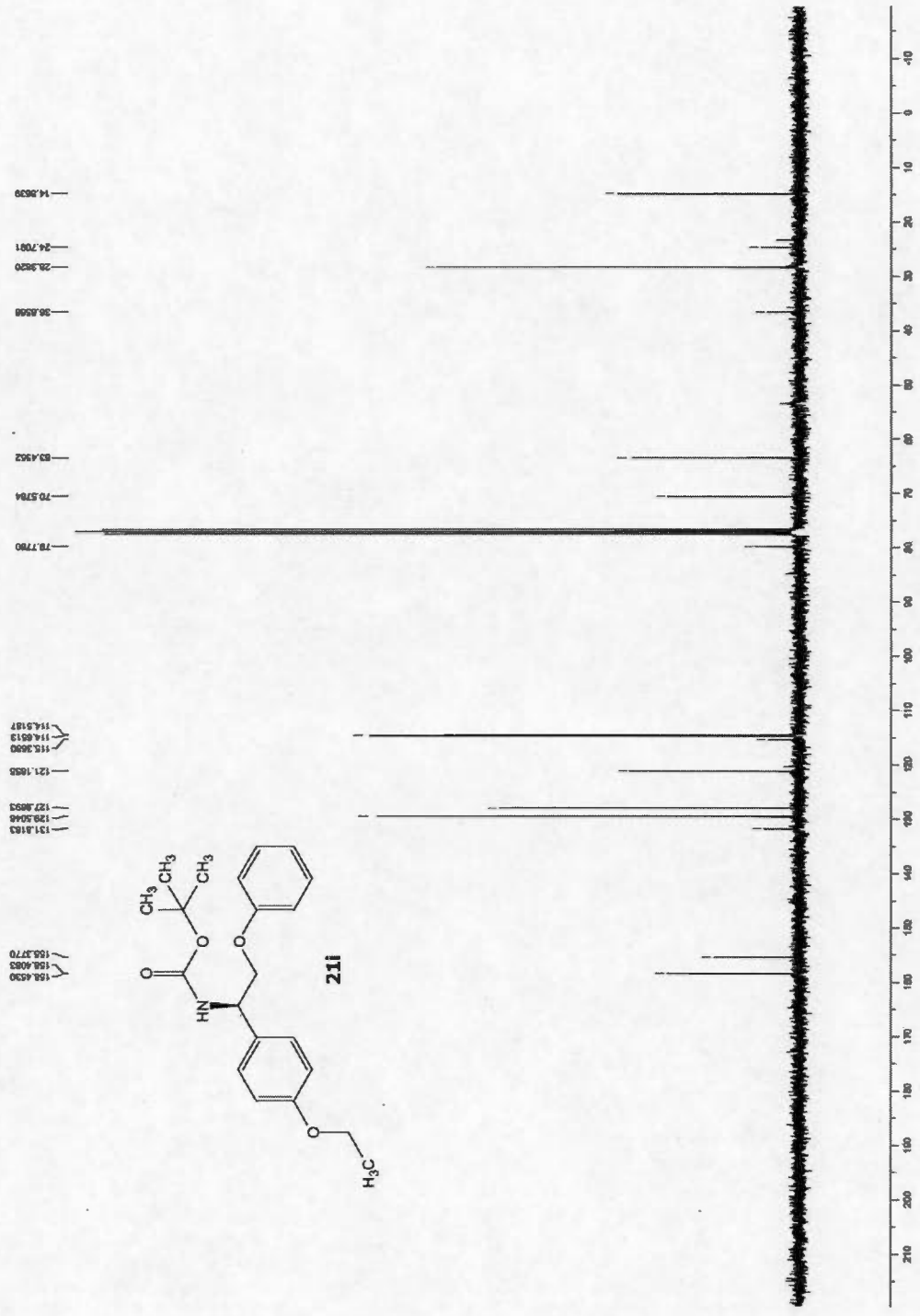

21g
%Transmission
Nombre d'onde (cm-1)
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
4000
3500
3000
2500
2000
1500
1000
500
3355,01
2976,63
2931,63
1689,14
1598,48
1585,12
1484,53
1451,40
1389,98
1365,38
1320,59
1288,17
1250,62
1184,92
1050,11
867,70
782,55
758,31
699,46
681,68

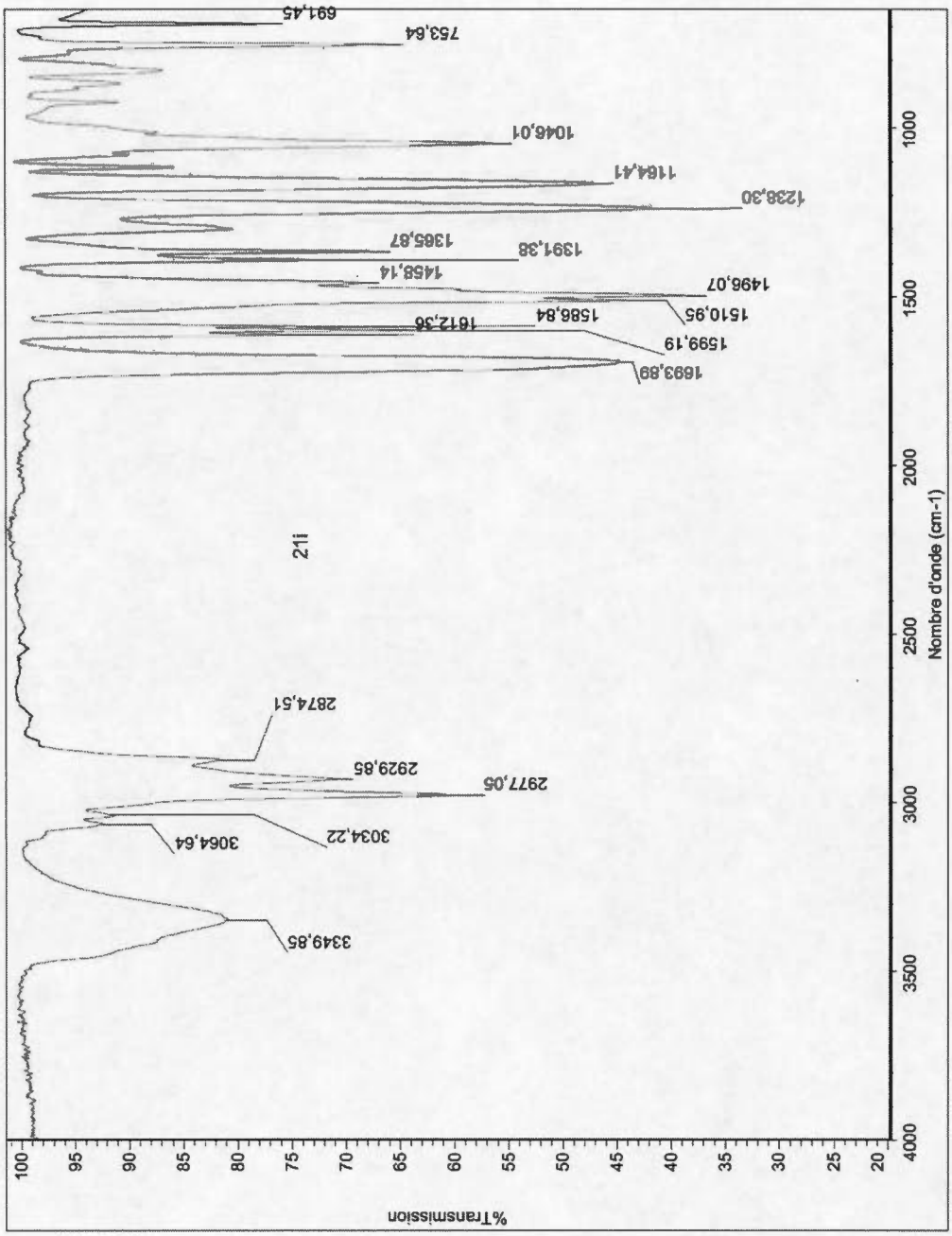

21h

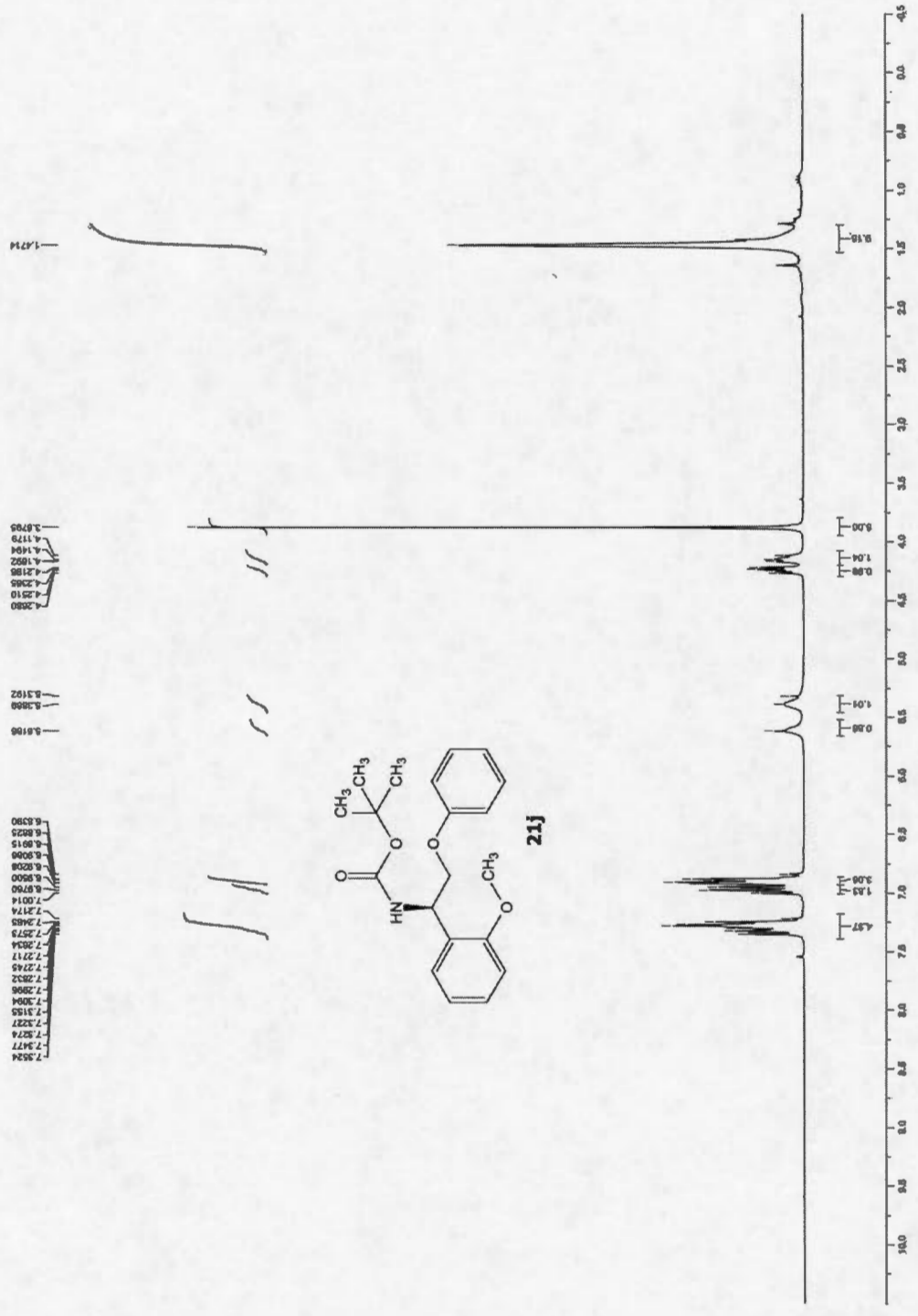
14.3191
28.3600
60.3374
70.7160
79.9450
112.8487
118.4795
118.7978
121.3688
127.7479
128.6538
129.5397
130.7829
135.9443
144.2506
158.3279
168.7523
166.8992
21h

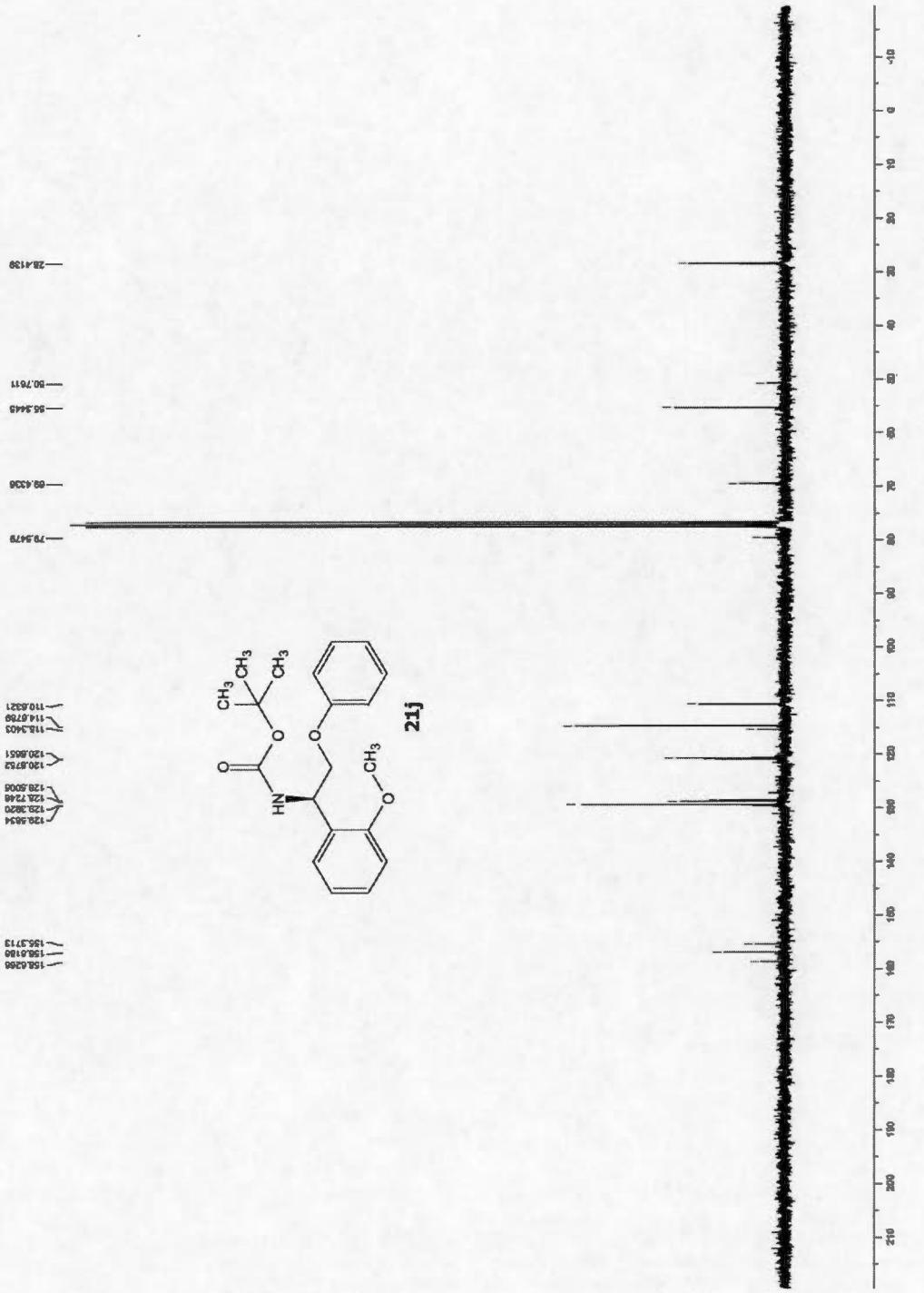

%Transmission
Nombre d'onde (cm-1)
21h
3350,98
2977,07
2931,77
1698,56
1637,08
1579,26
1492,40
1444,96
1380,79
1365,49
1308,13
1245,83
1159,52
1094,51
1030,16
981,04
859,93
780,50
736,28
698,91
678,84

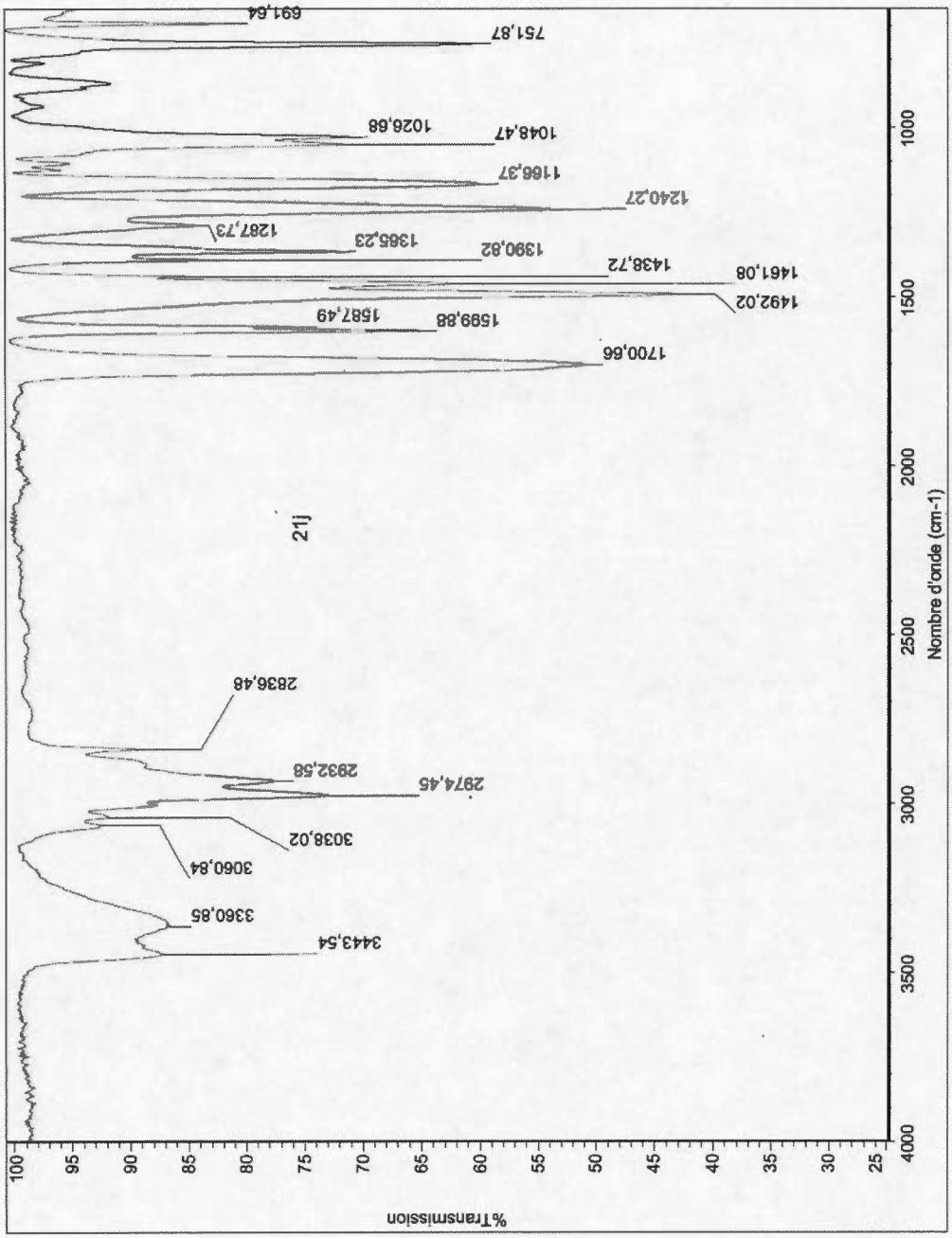

21i
CH3
CH3
CH3
O
O
O
HN
H3C

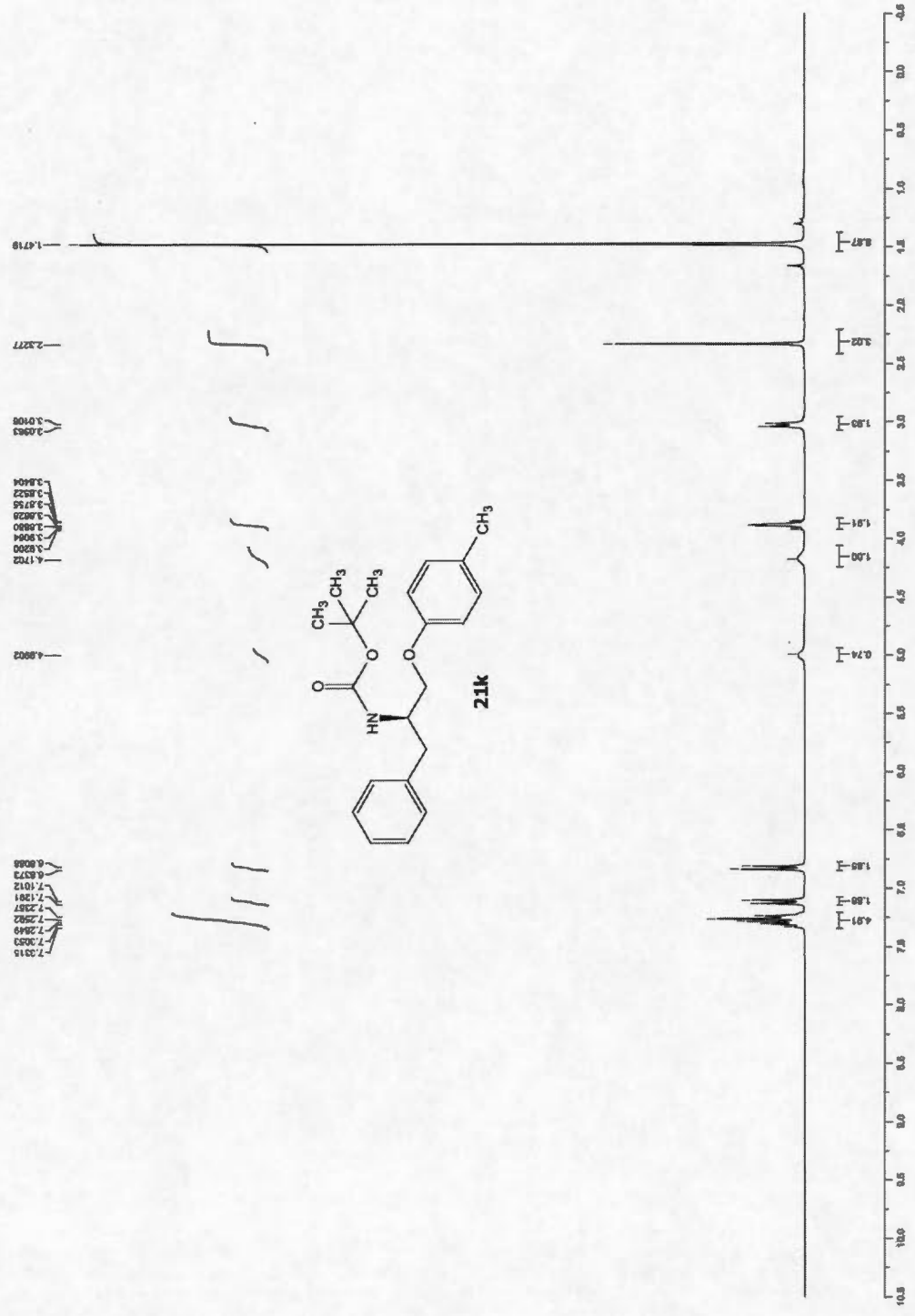

14.8539
24.7091
28.3820
36.8598
63.4962
70.5784
78.7780
115.3690
114.8513
114.5187
121.1838
127.8853
129.5046
131.8183
155.4530
156.4083
156.3770
21i
CH3
CH3
CH3
O
O
O
HN
O
H3C

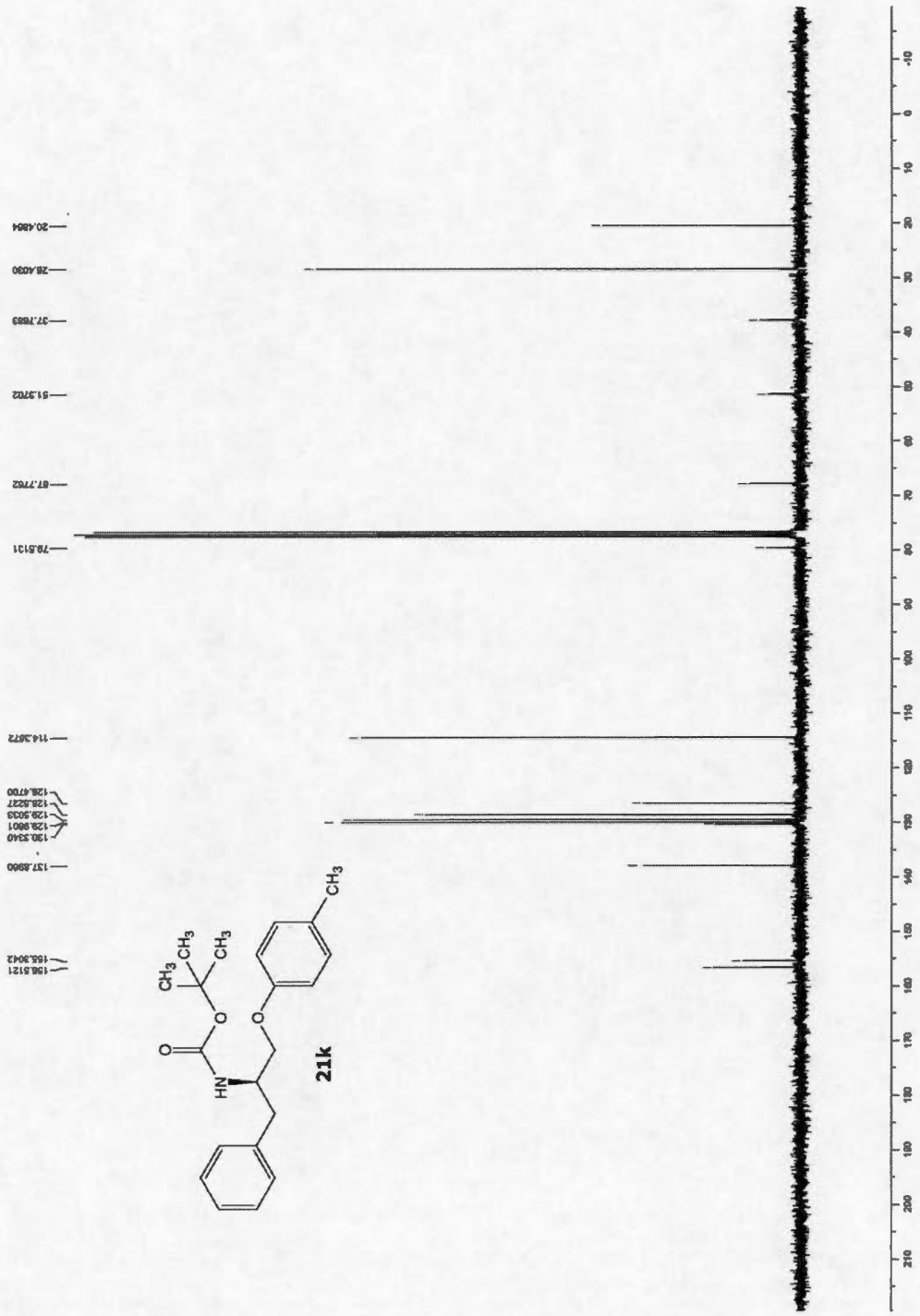

691,45
753,64
1046,01
1164,41
1238,30
1391,38
1365,87
1458,14
1496,07
1510,95
1586,84
1612,36
1599,19
1693,89
211
2874,51
2929,85
2977,05
3034,22
3064,64
3349,85
%Transmission
Nombre d'onde (cm-1)

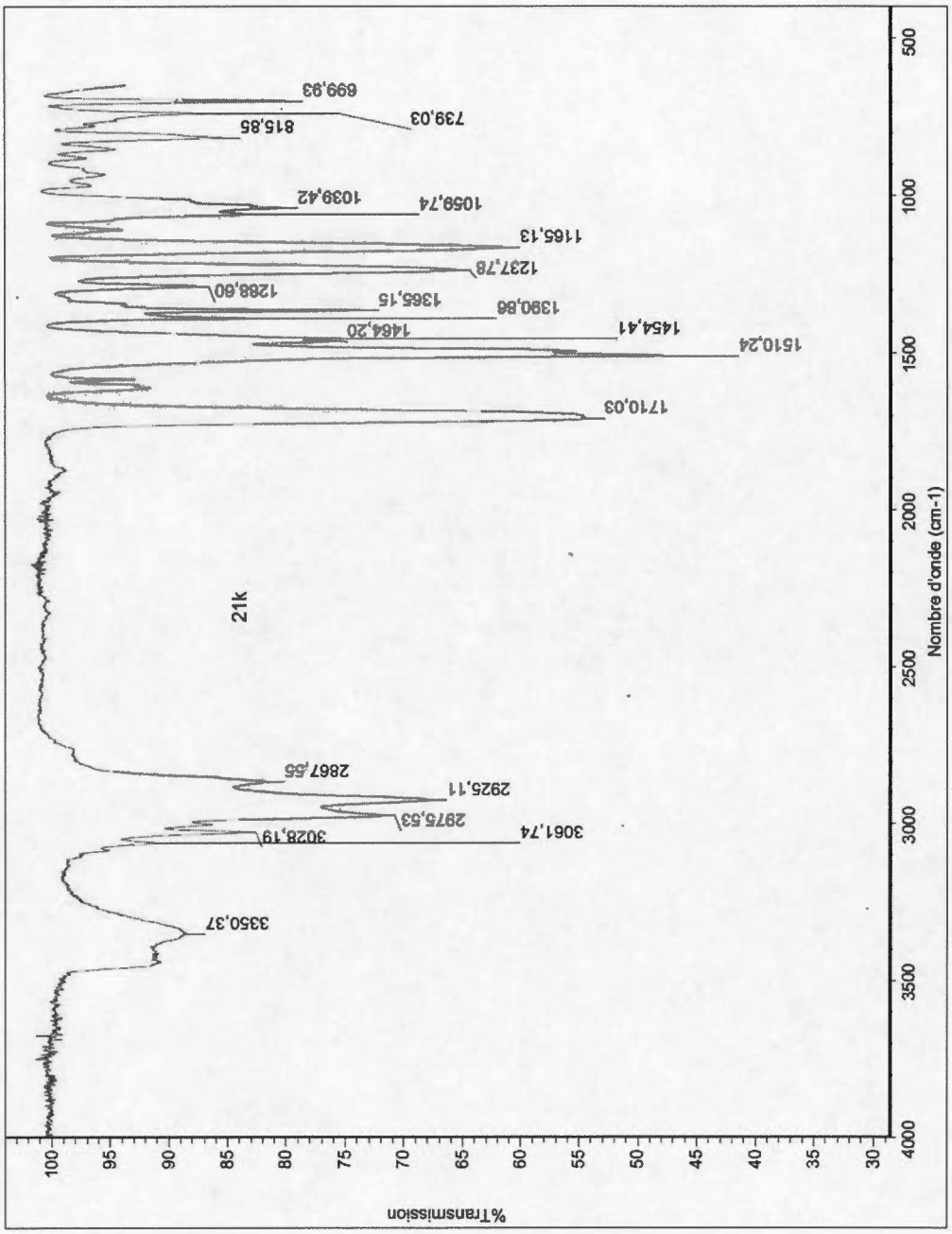

21j

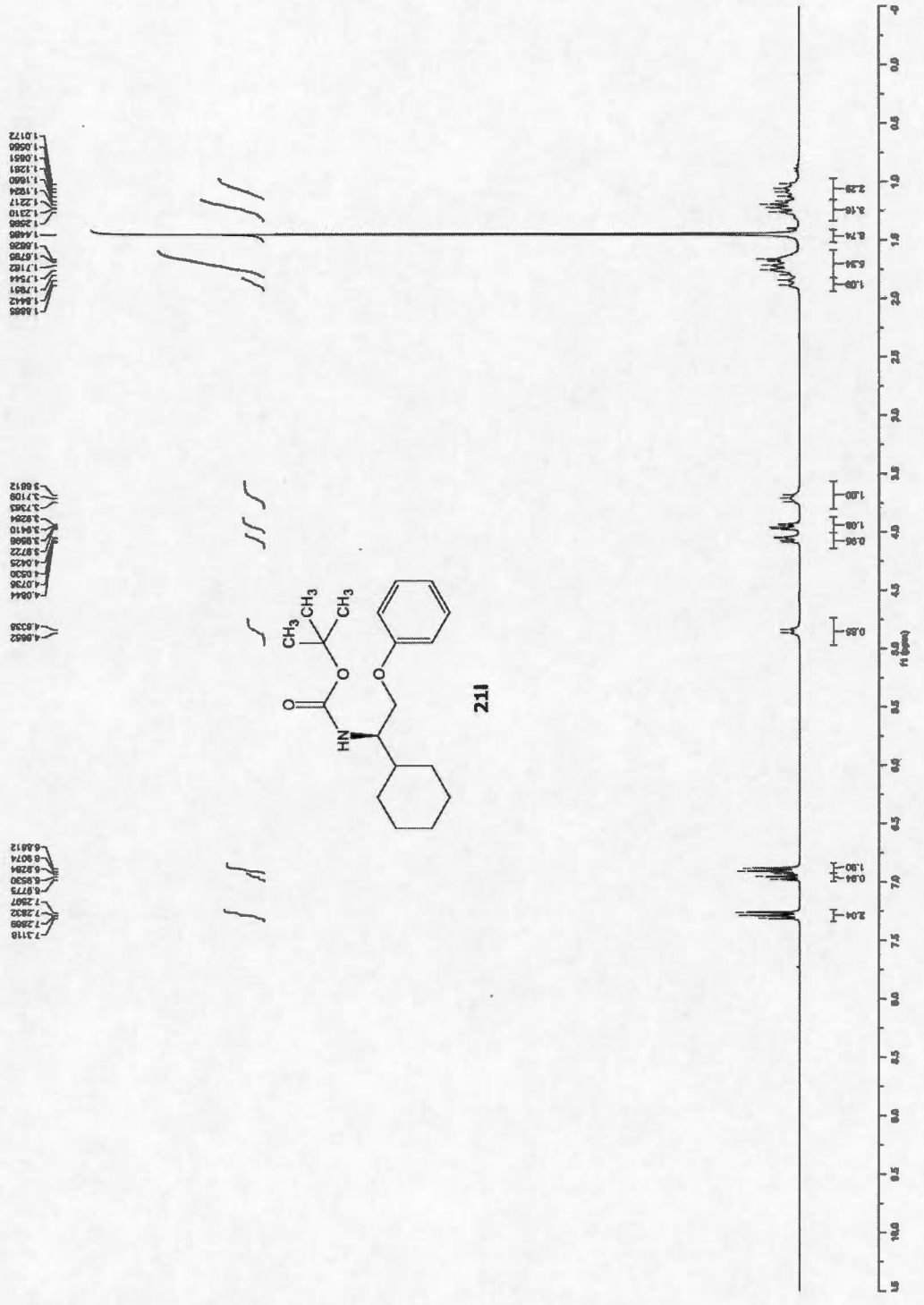

28.4139
60.7611
66.4336
79.5479
110.6321
114.8789
118.3403
120.8751
120.8851
128.5006
128.5054
128.7248
128.3820
158.6180
158.6366
155.3713
21j


21j
%Transmission
Nombre d'onde (cm-1)
691,64
751,87
1026,68
1048,47
1166,37
1240,27
1287,73
1365,23
1390,82
1438,72
1461,08
1492,02
1587,49
1589,88
1700,66
2836,48
2932,58
2974,45
3038,02
3060,84
3360,85
3443,54


21k

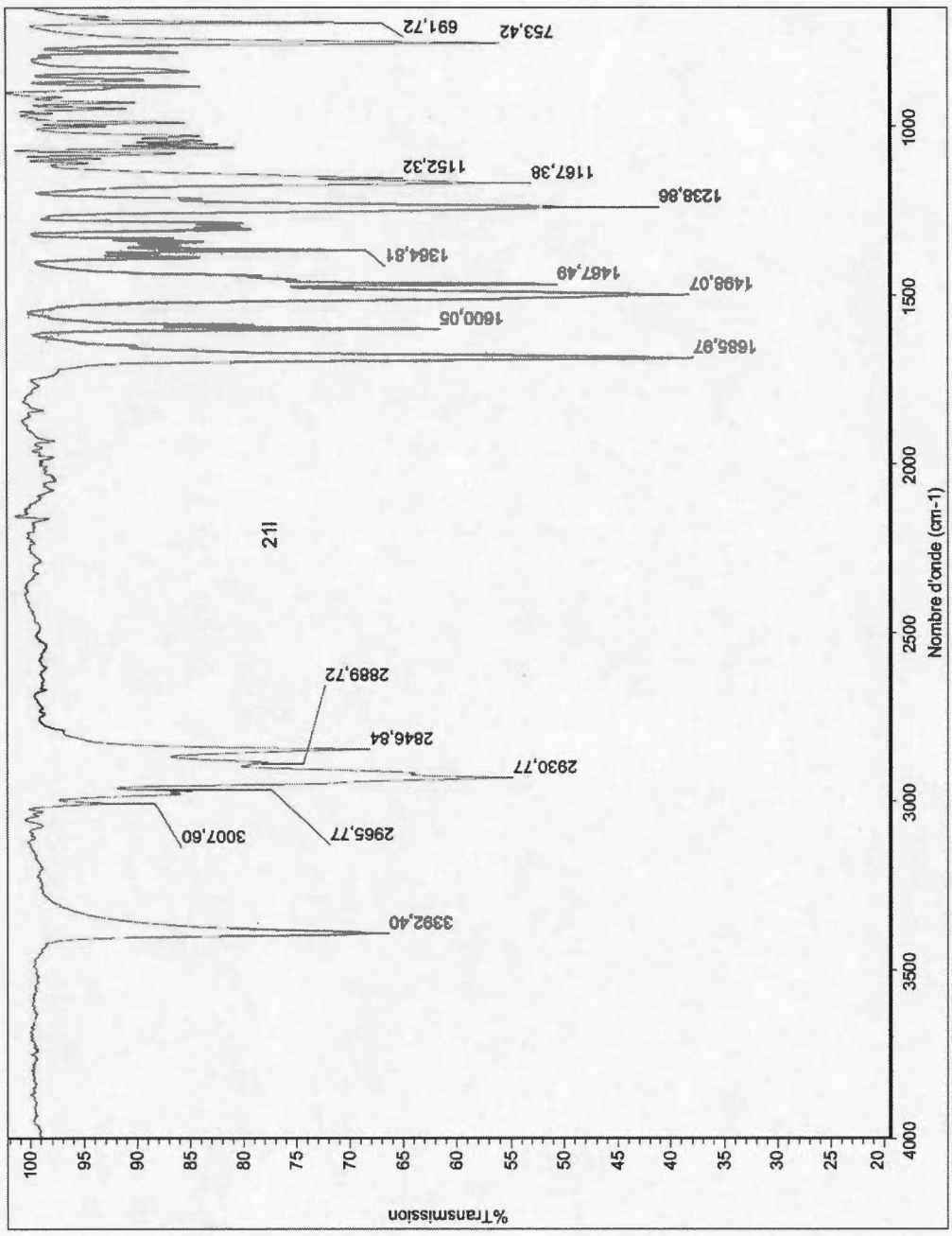

20.4864
28.4030
37.7883
51.3702
67.7762
78.5131
114.3572
130.3340
129.3801
129.3035
128.3237
128.4700
137.4900
155.3042
156.5121
21k

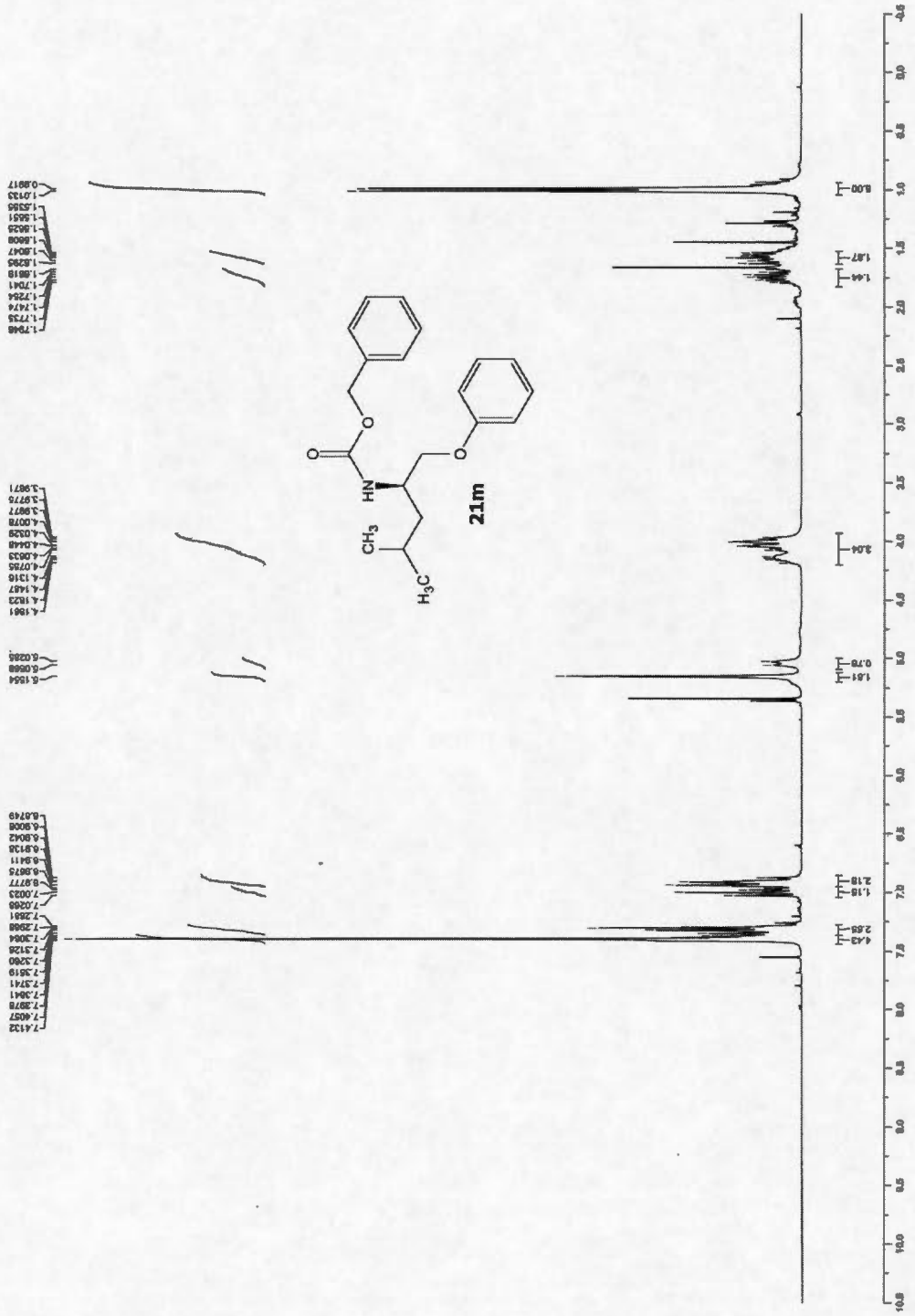

%Transmission
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
4000
3500
3000
2500
2000
1500
1000
500
Nombre d'onde (cm-1)
21k
3350,37
3061,74
3028,19
2975,53
2925,11
2867,55
1710,03
1510,24
1454,41
1464,20
1390,86
1365,15
1288,60
1237,78
1165,13
1059,74
1039,42
815,85
739,03
699,93

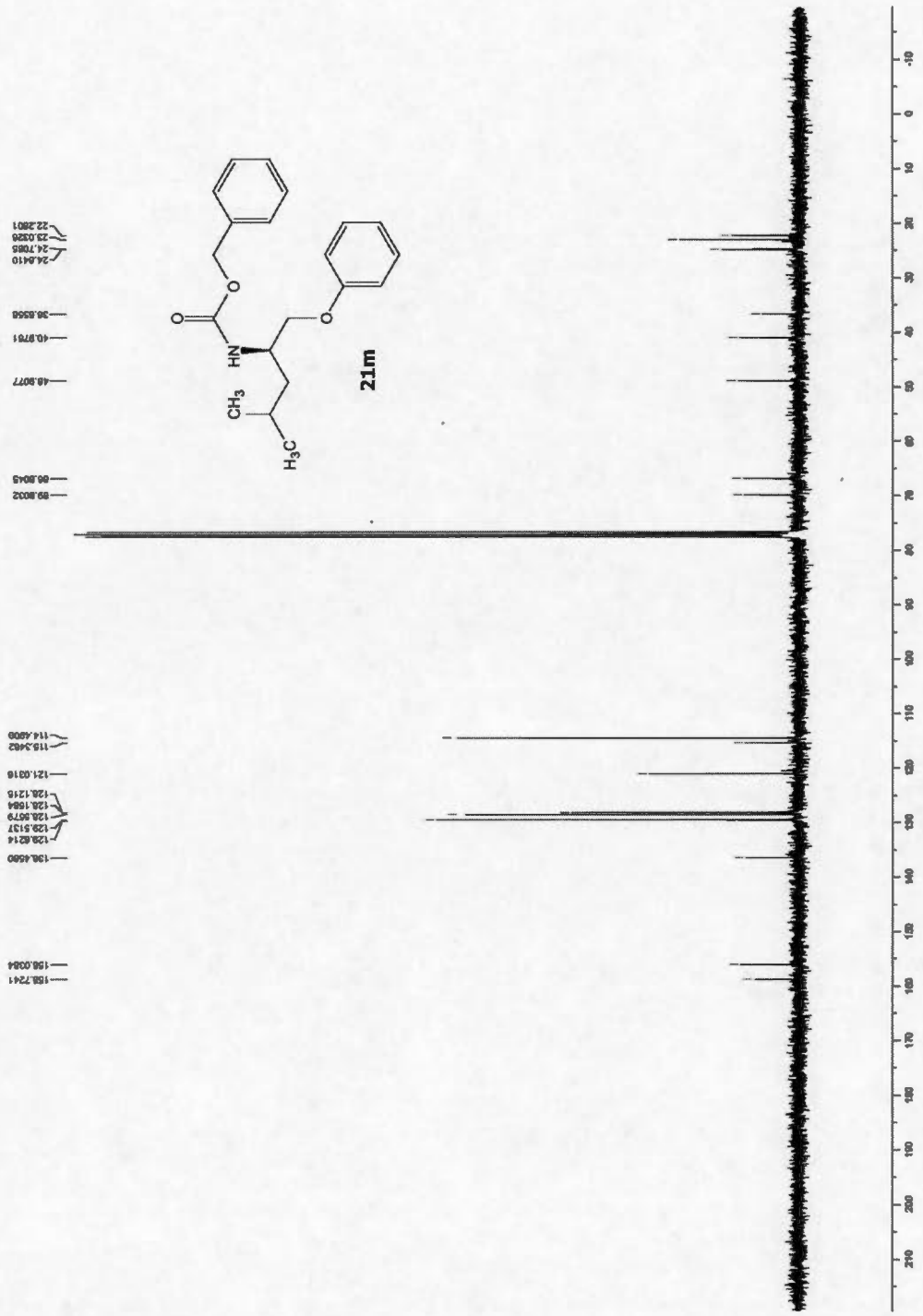

CH3
CH3
CH3
O
O
O
HN
211

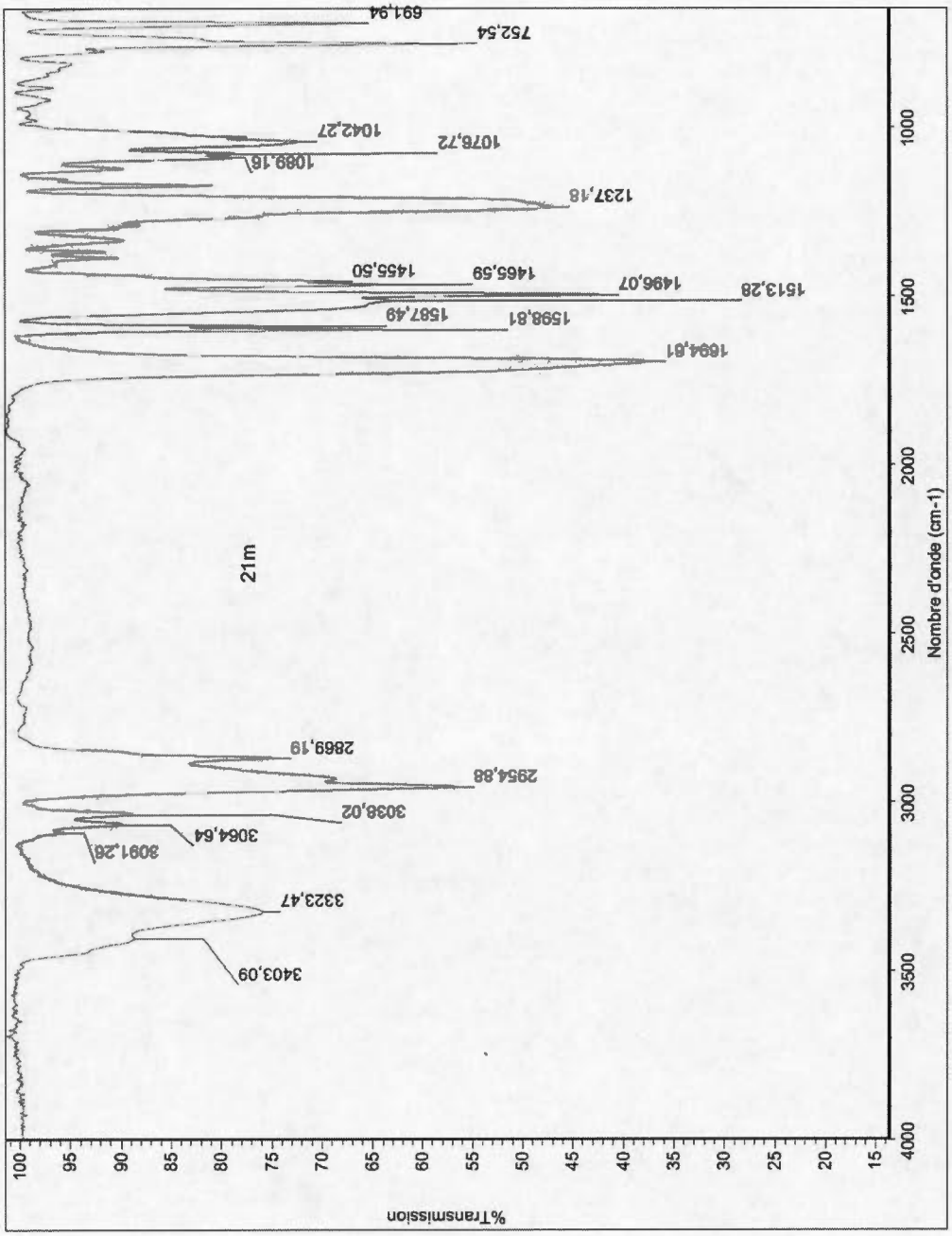
155.8024
155.8173
128.4724
120.9863
114.4637
79.2863
77.4598
77.0403
76.8171
67.6869
64.8257
39.6238
29.8533
29.2956
28.4317
28.3046
28.1361
24.7068
f1 (ppm)

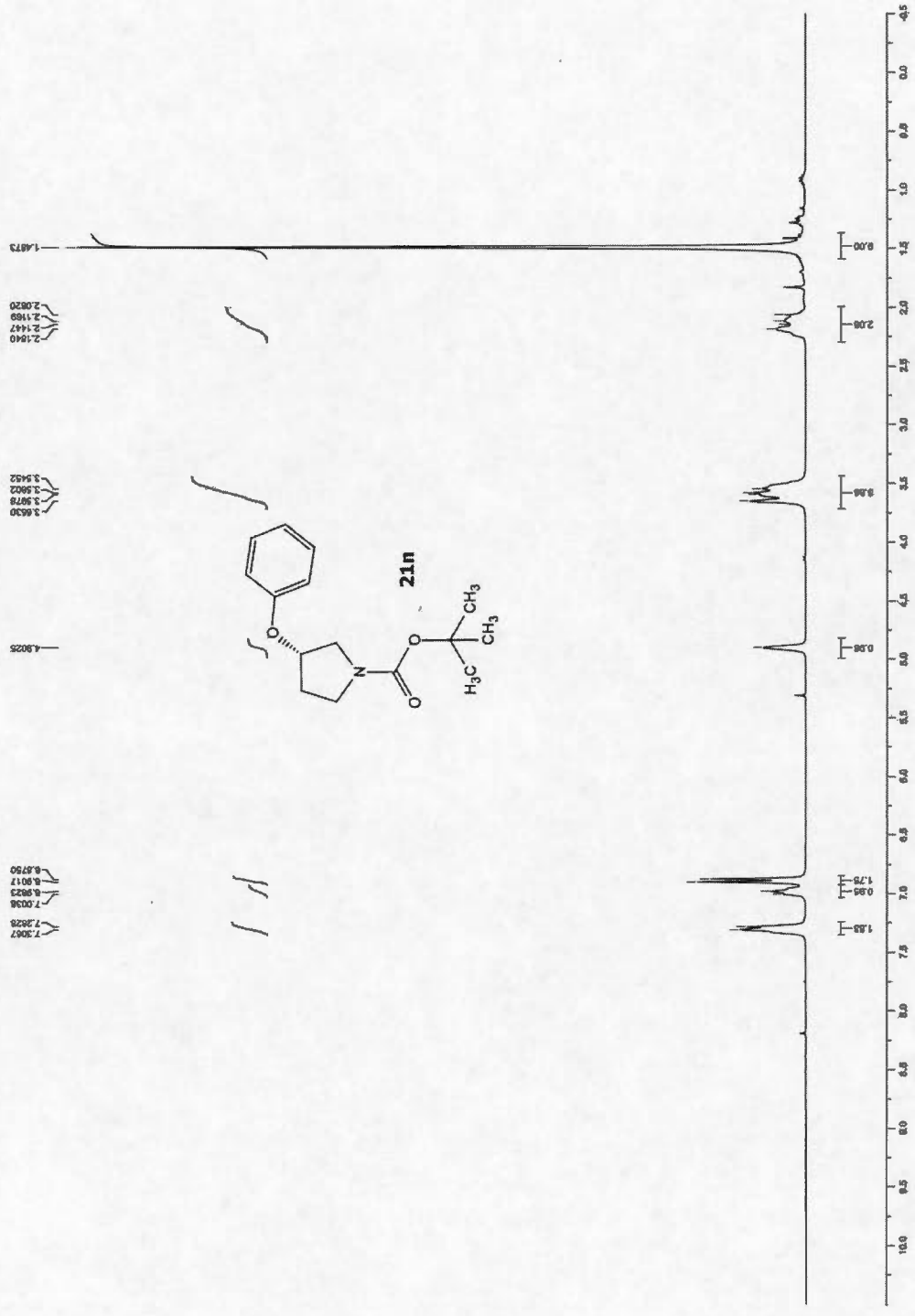
21l


%Transmission
Nombre d'onde (cm-1)
211
3392,40
3007,60
2965,77
2930,77
2889,72
2846,84
1685,97
1600,05
1498,07
1467,49
1384,81
1238,86
1167,38
1152,32
753,42
691,72

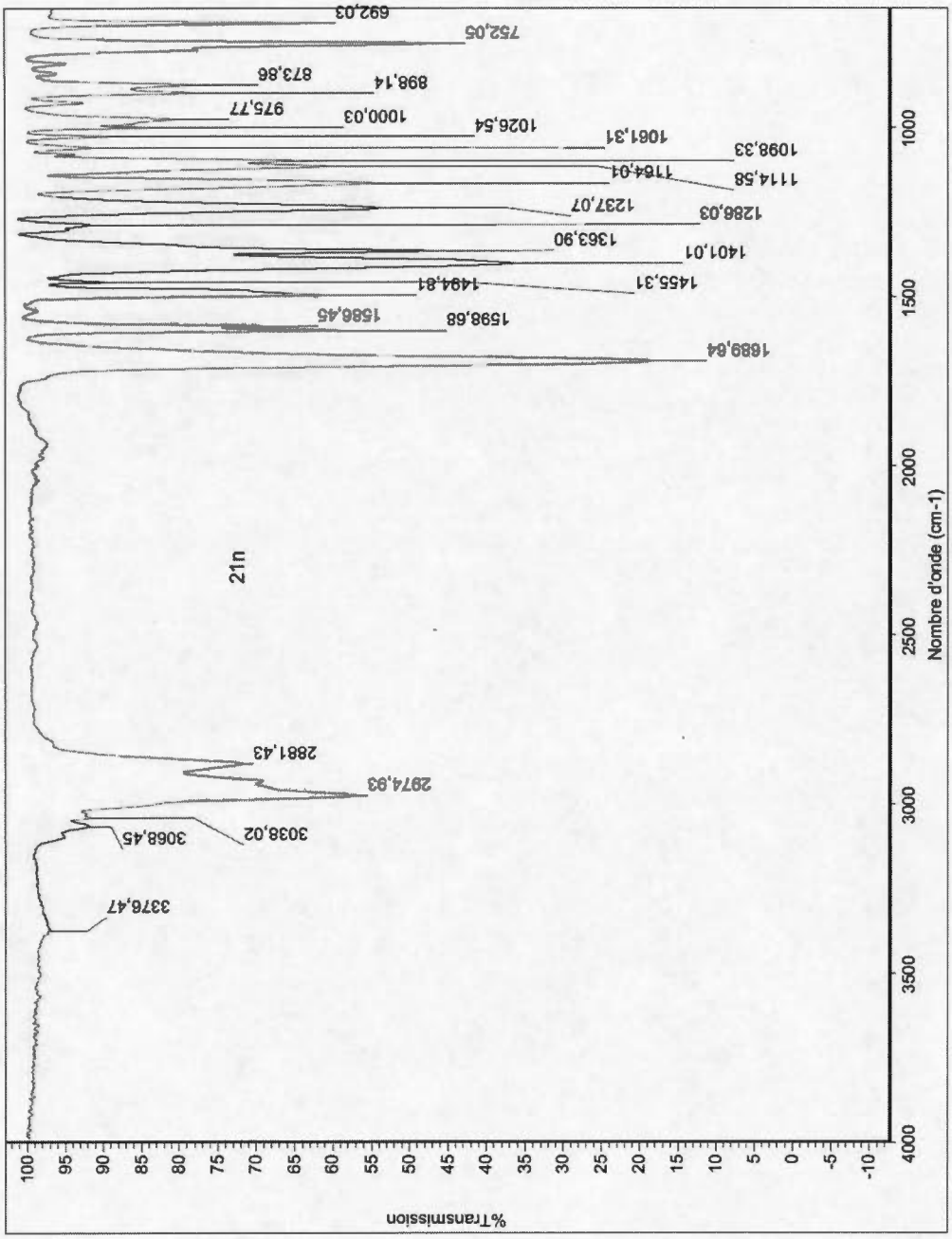

21m
HN
CH3
H3C

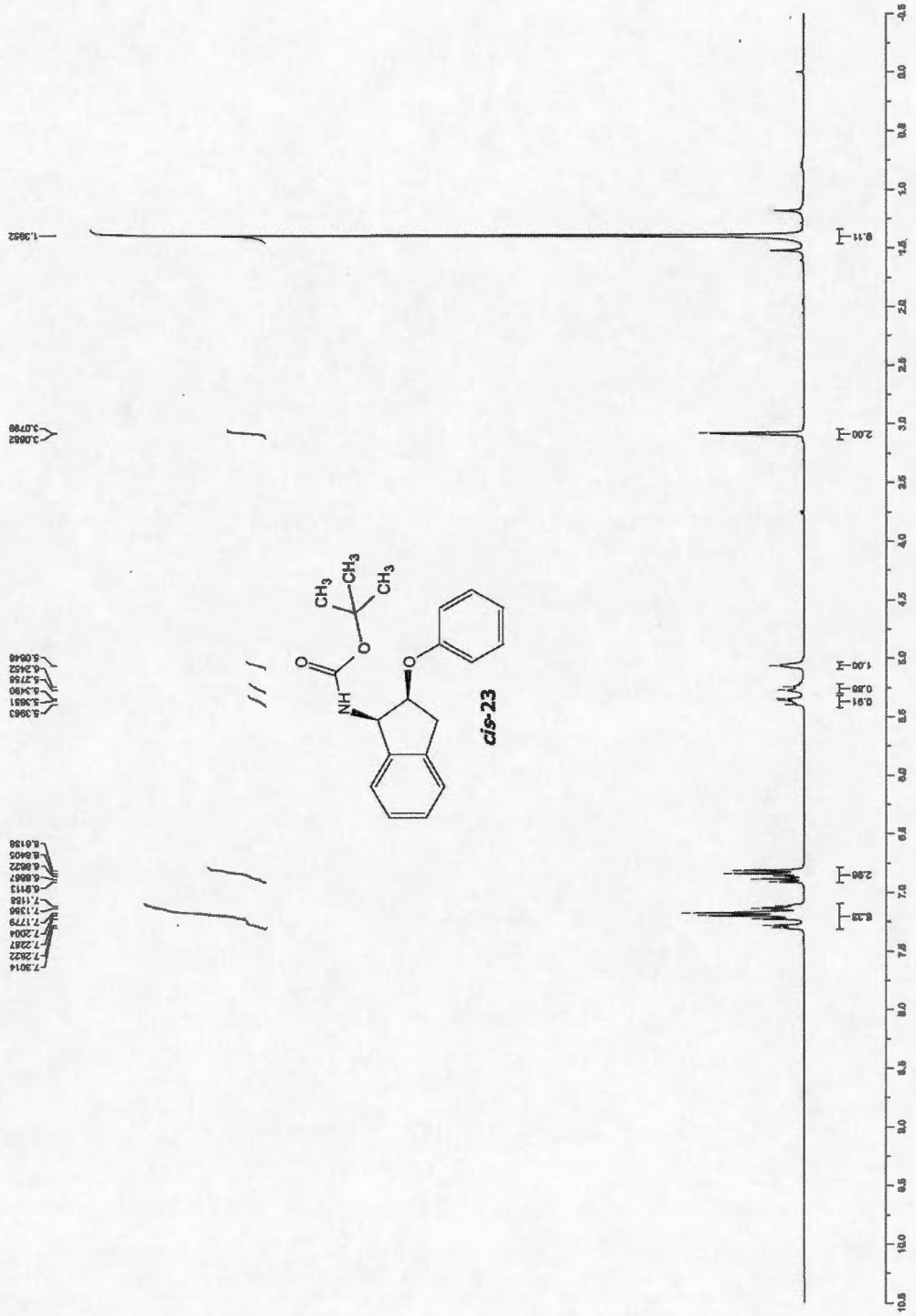

21m
HN
O
O
O
CH3
H3C
22.2801
23.0326
24.7065
24.8410
36.8556
40.8781
48.8077
86.8043
89.8032
114.4808
115.3482
121.0316
128.1215
128.1584
128.8079
129.5137
129.8214
136.4580
156.0284
156.7241

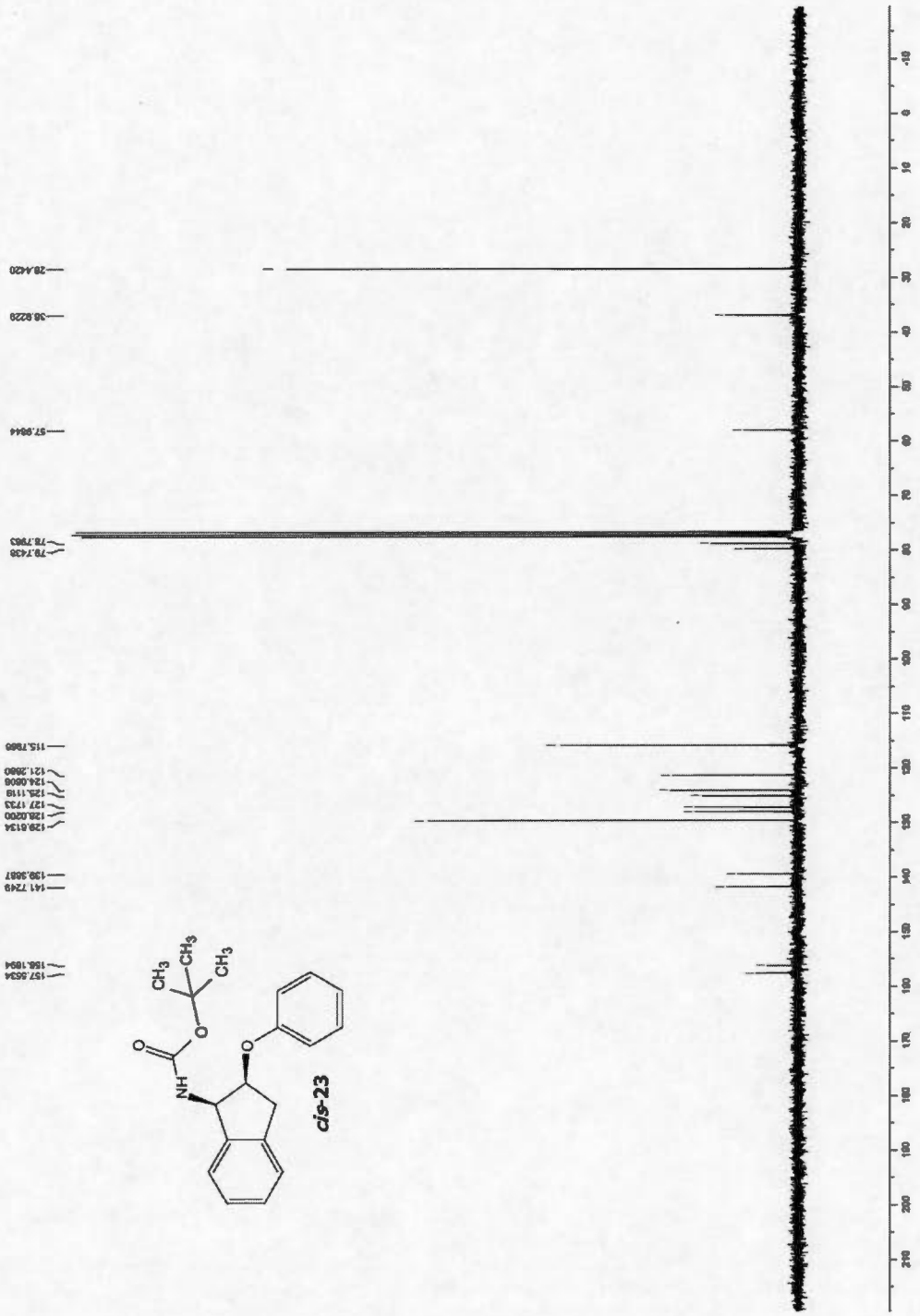

%Transmission
Nombre d'onde (cm-1)
21m
3403,09
3323,47
3091,26
3064,64
3038,02
2954,88
2869,19
1694,81
1598,81
1587,49
1513,28
1496,07
1465,59
1455,50
1237,18
1089,16
1078,72
1042,27
752,54
691,94

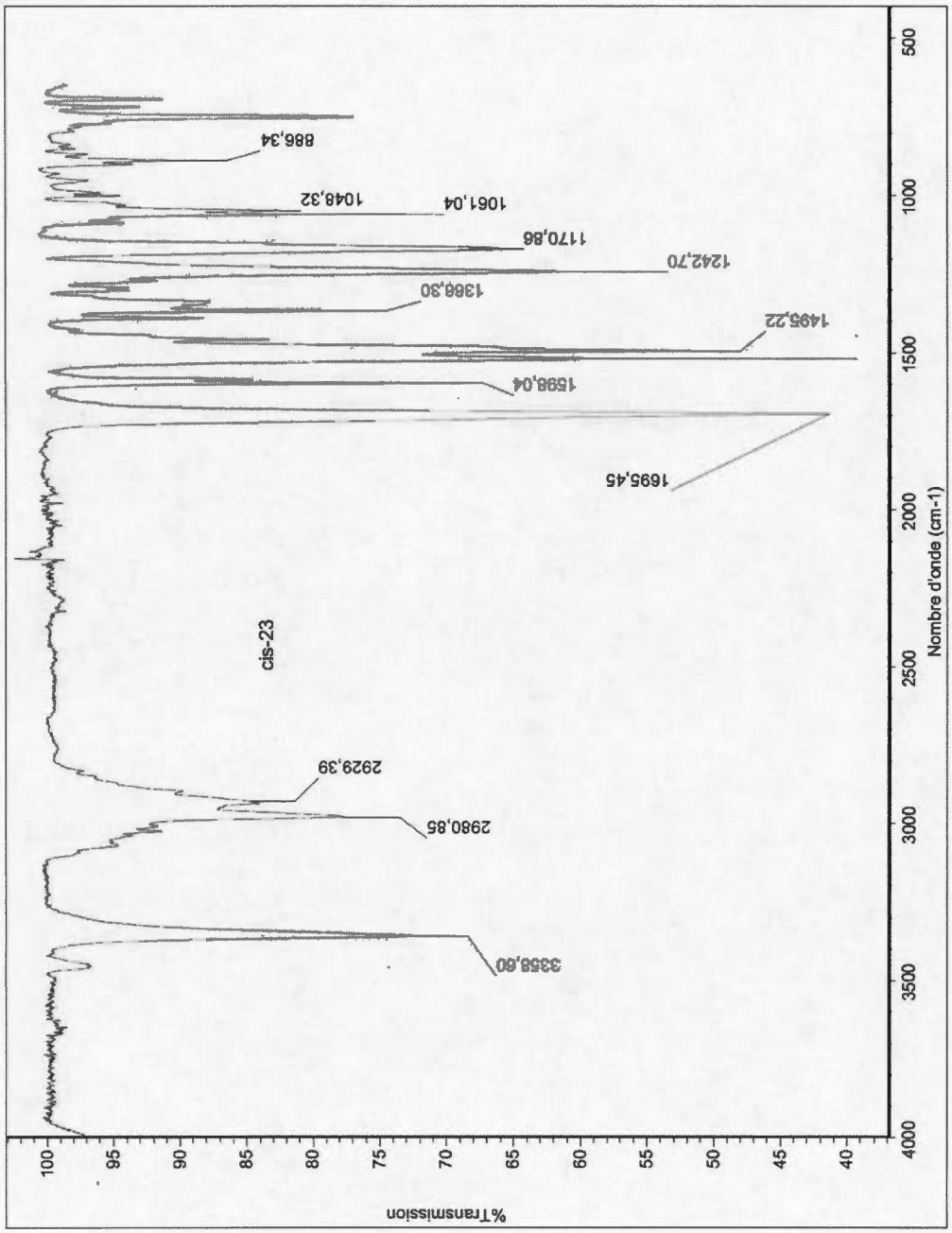

21n
O
N
O
O
CH3
CH3
H3C
1.4873
2.1840
2.1447
2.1169
2.0820
3.6630
3.5978
3.5802
3.5462
4.8025
7.3067
7.2828
7.0036
6.9825
6.8017
6.8750
8.00
2.08
3.06
0.96
1.73
0.86
1.88

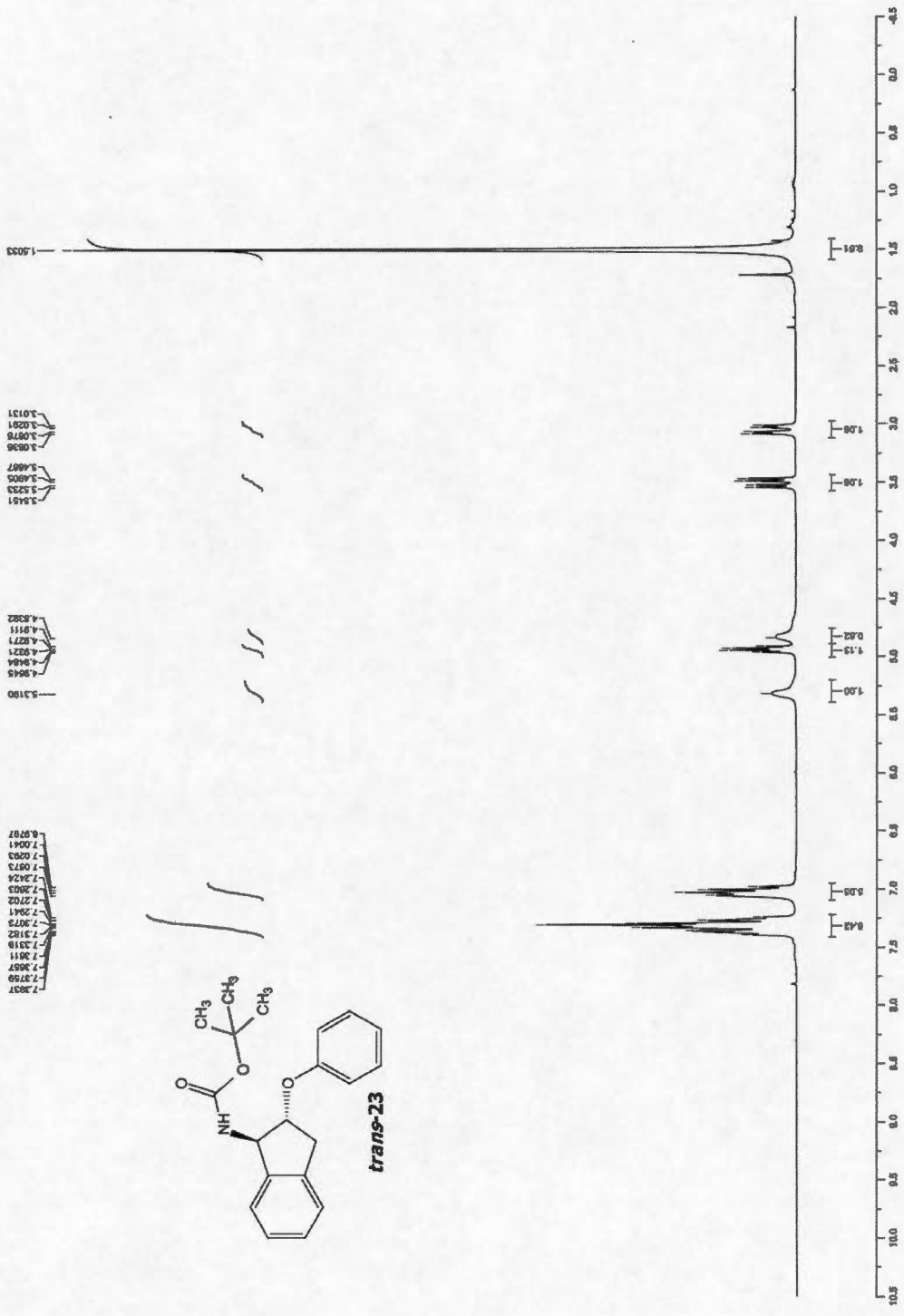

28.5232
30.7643
31.5317
43.7668
44.1283
51.3057
51.6868
75.8108
76.2800
79.4410
113.6487
121.1369
129.8103
154.3568
157.1478
21n
O
N
O
O
H_3C
CH_3
CH_3

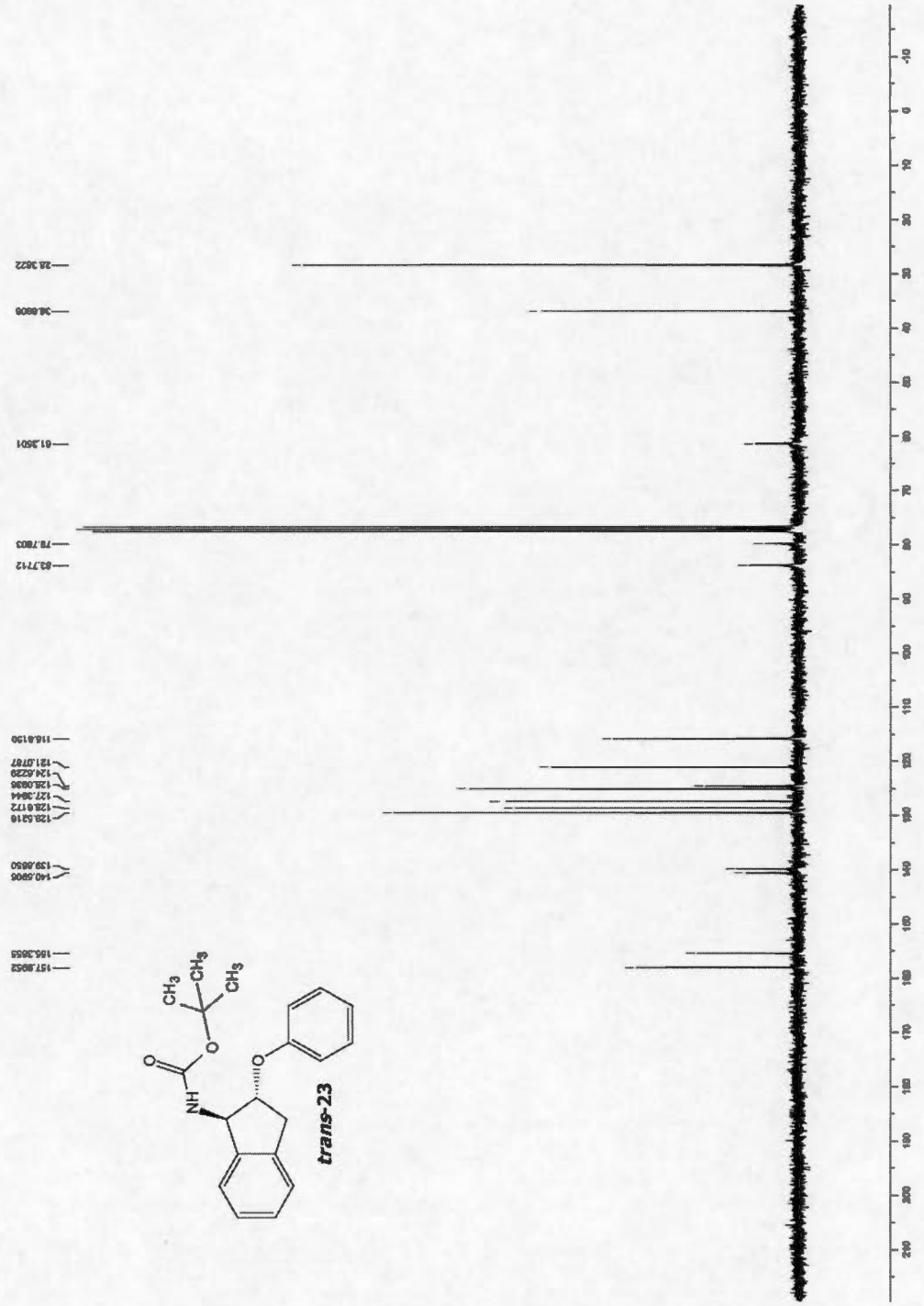

%Transmission
Nombre d'onde (cm-1)
21n
3376,47
3068,45
3038,02
2974,83
2881,43
1689,64
1598,68
1586,45
1494,81
1455,31
1401,01
1363,90
1286,03
1237,07
1114,58
1098,33
1061,31
1026,54
1000,03
975,77
898,14
873,86
752,05
692,03

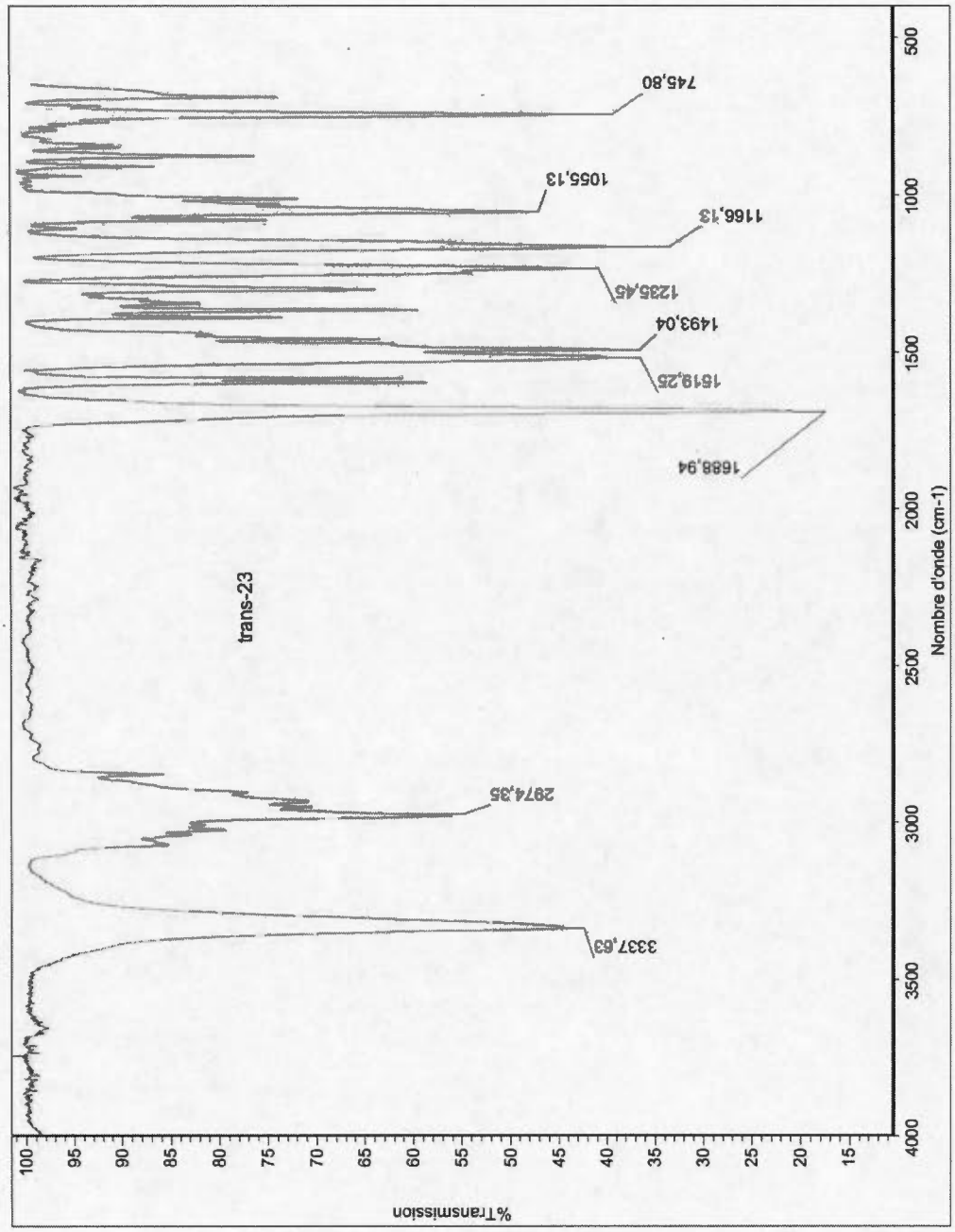

cis-23

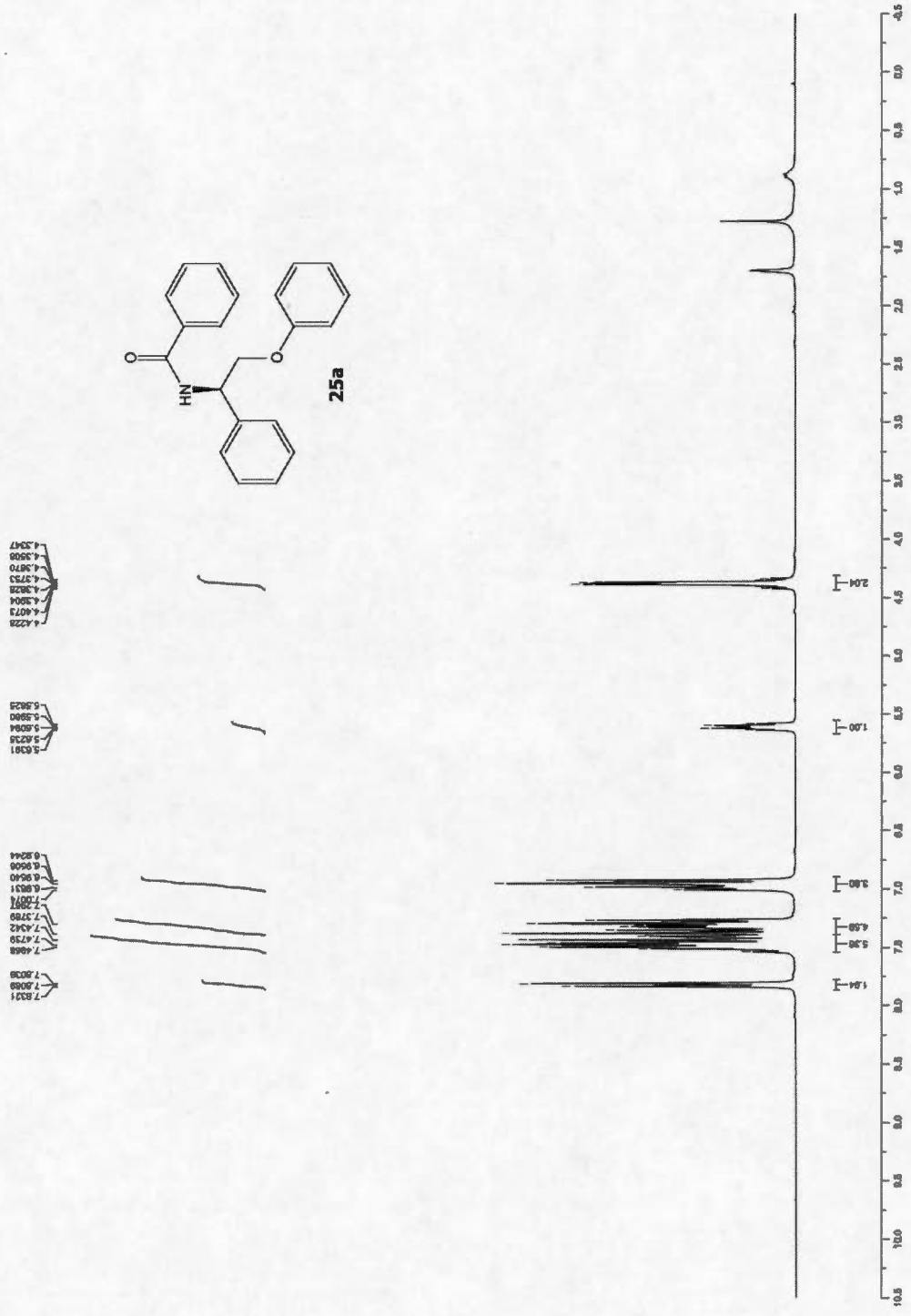

28.4420
36.8229
57.9844
78.7435
78.7965
115.7860
121.2860
124.0808
125.1118
127.1723
128.0200
129.8134
139.3087
141.7249
157.9534
158.1894
CH3
CH3
CH3
O
O
NH
O
cis-23

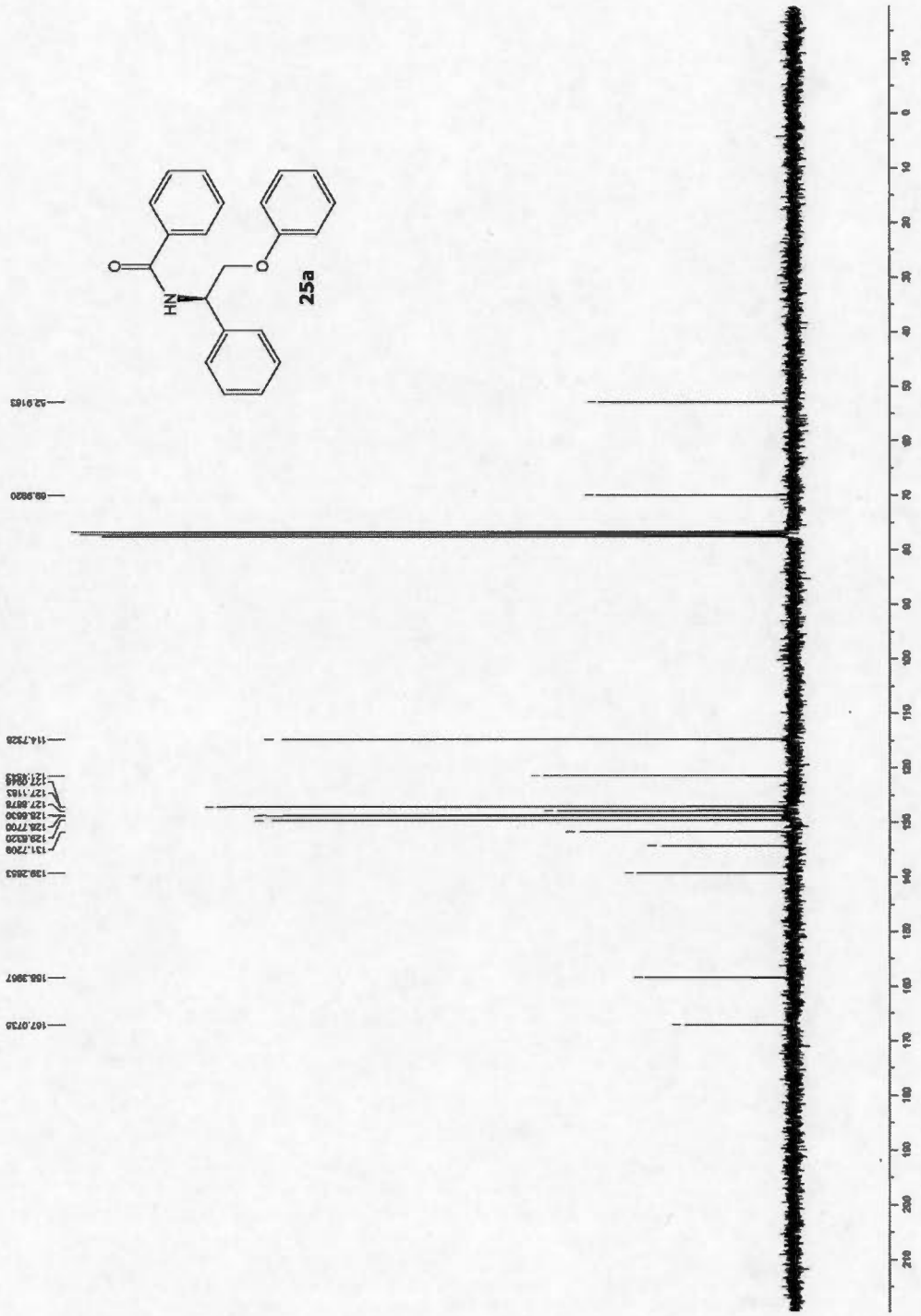

%Transmission
Nombre d'onde (cm-1)
cis-23
3358,60
2980,85
2929,39
1695,45
1598,04
1495,22
1368,30
1242,70
1170,86
1061,04
1048,32
886,34

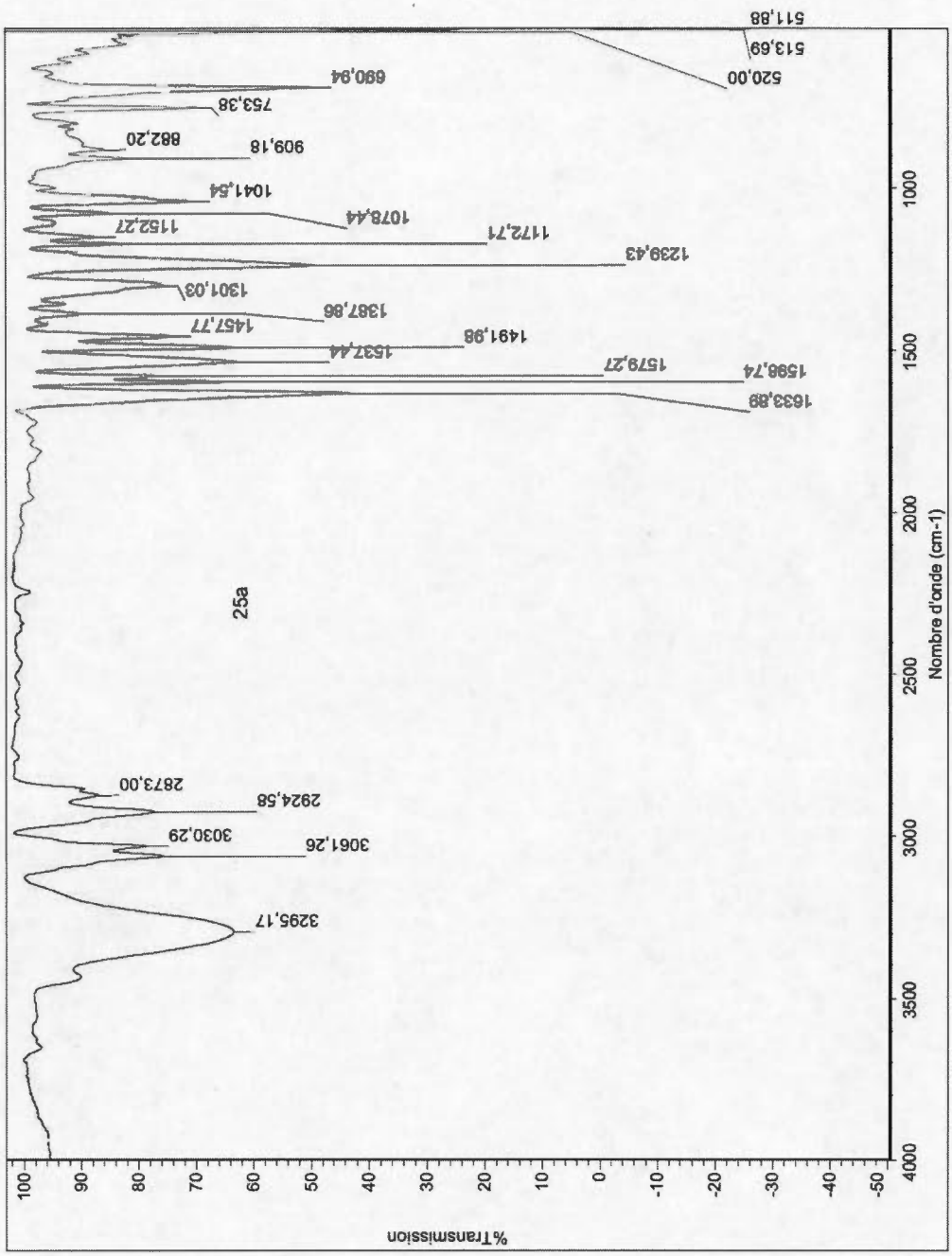

trans-23

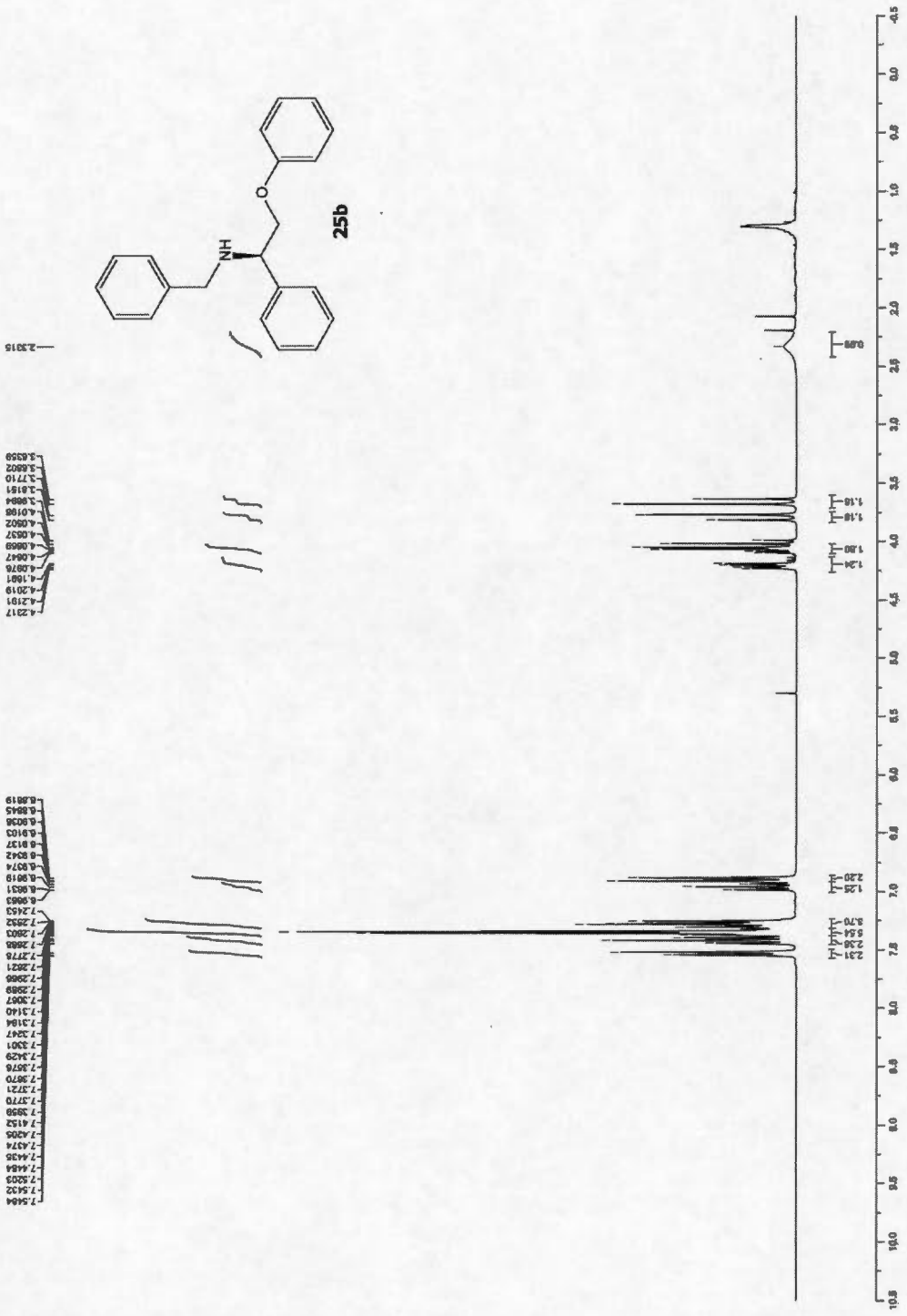

28.3622
36.8806
61.3501
78.7803
83.7712
118.8130
121.0787
124.6229
126.0936
127.3844
128.6172
128.6218
139.0850
140.5806
157.8052
165.3653
trans-23

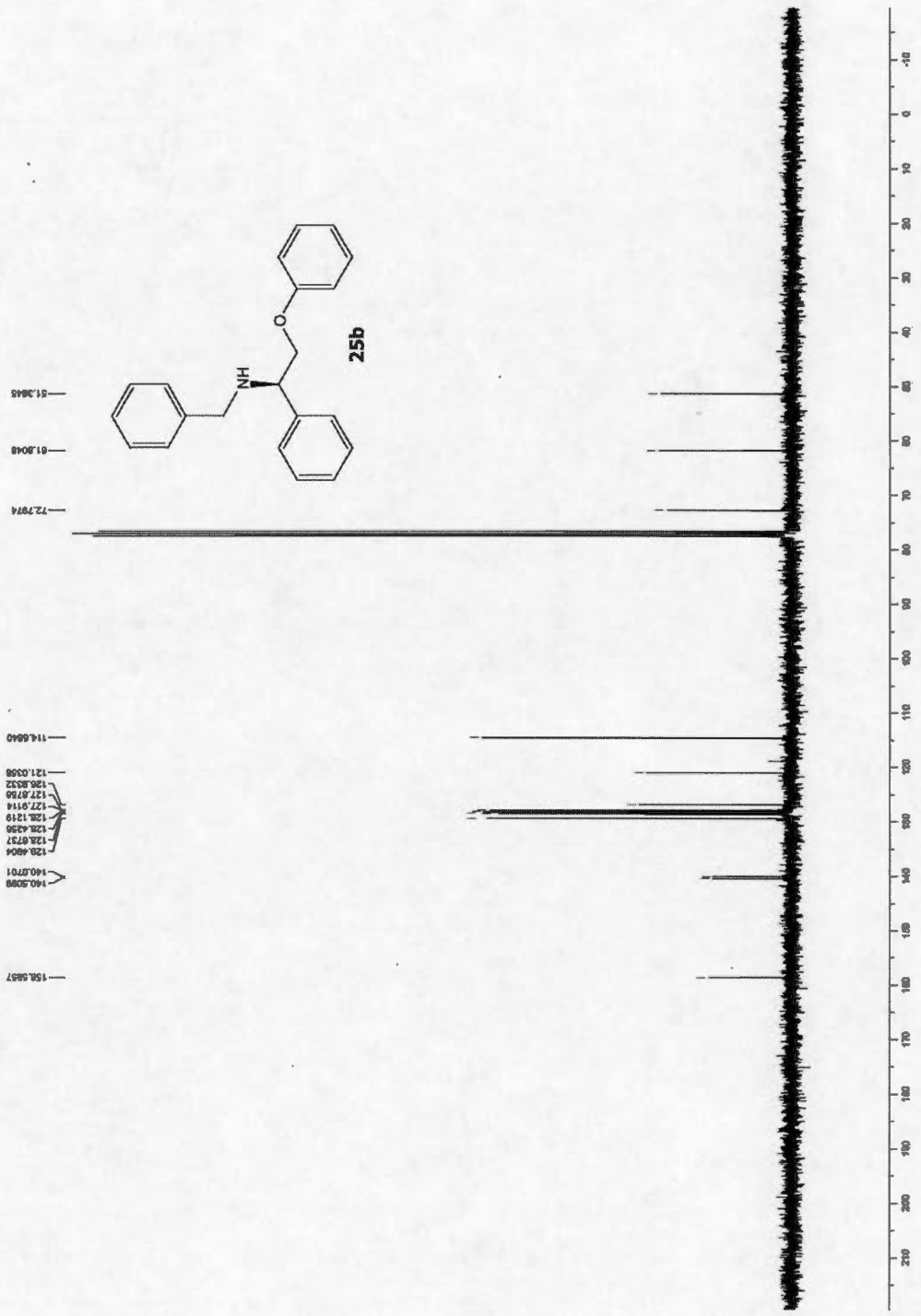

%Transmission
Nombre d'onde (cm-1)
trans-23
3337,63
2874,35
1688,94
1619,25
1493,04
1235,45
1166,13
1055,13
745,80

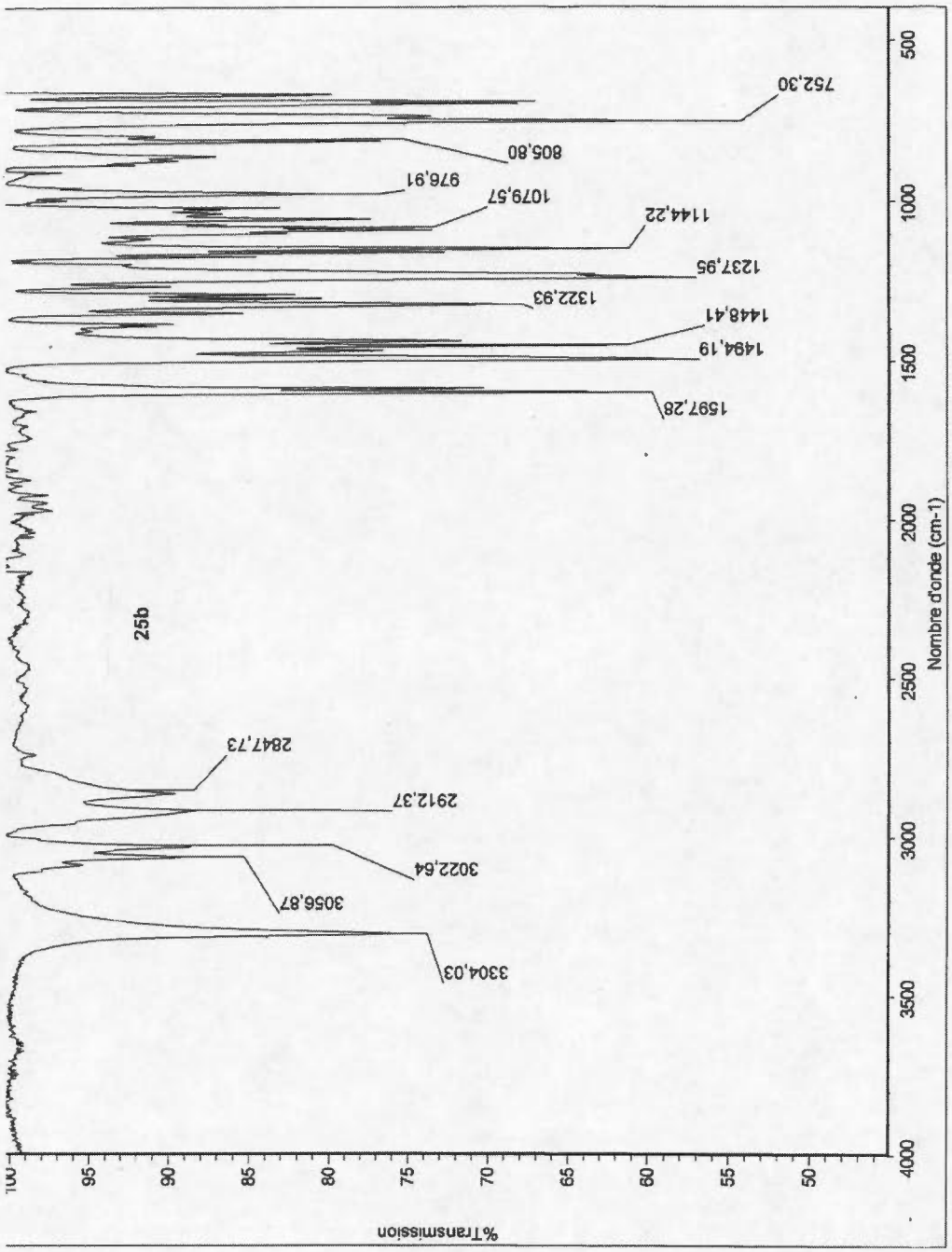

25a

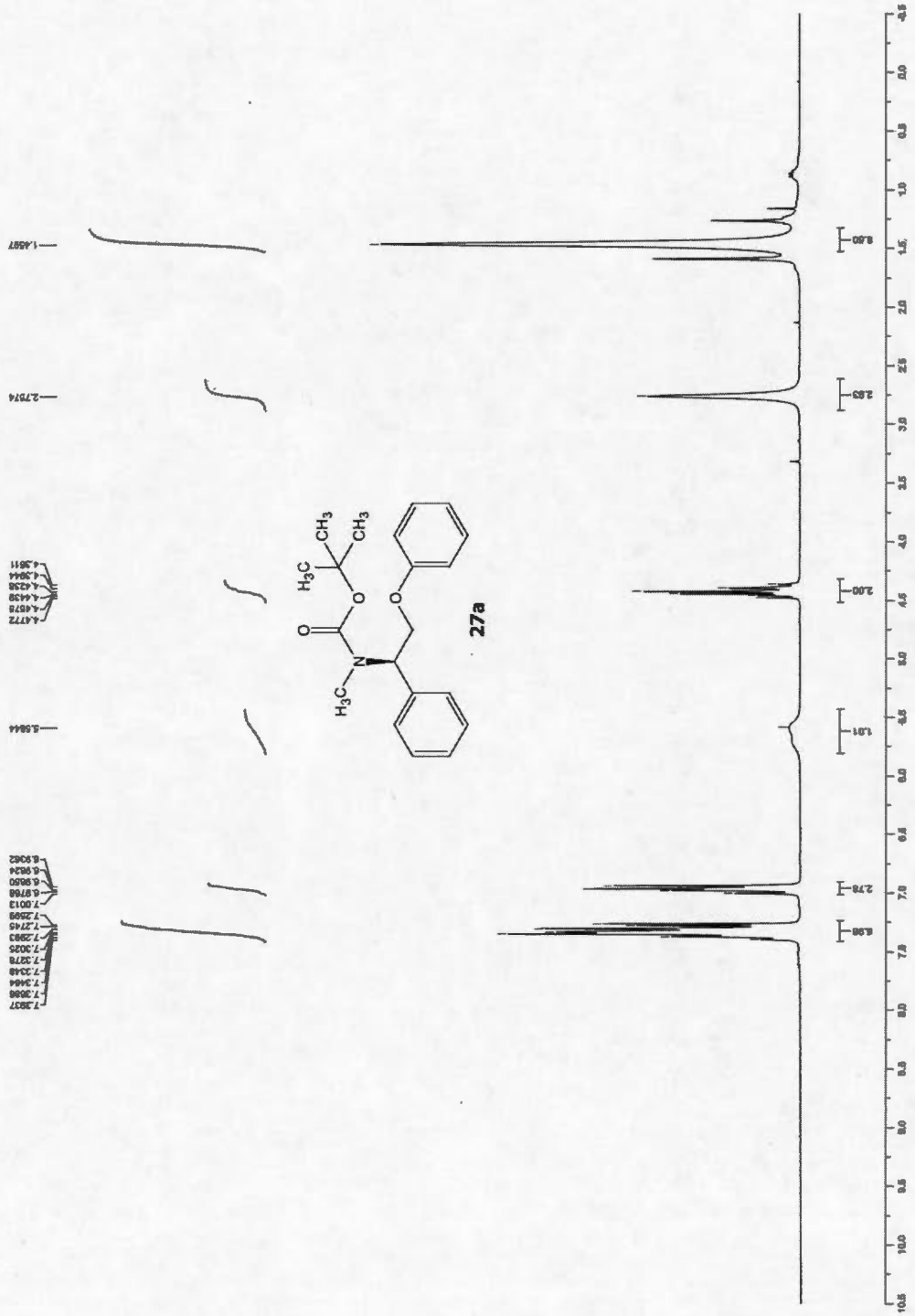

25a
52.9163
69.9820
114.7326
127.8846
127.1163
127.8878
128.6630
128.7700
129.6220
131.7709
139.2663
158.3867
167.0736

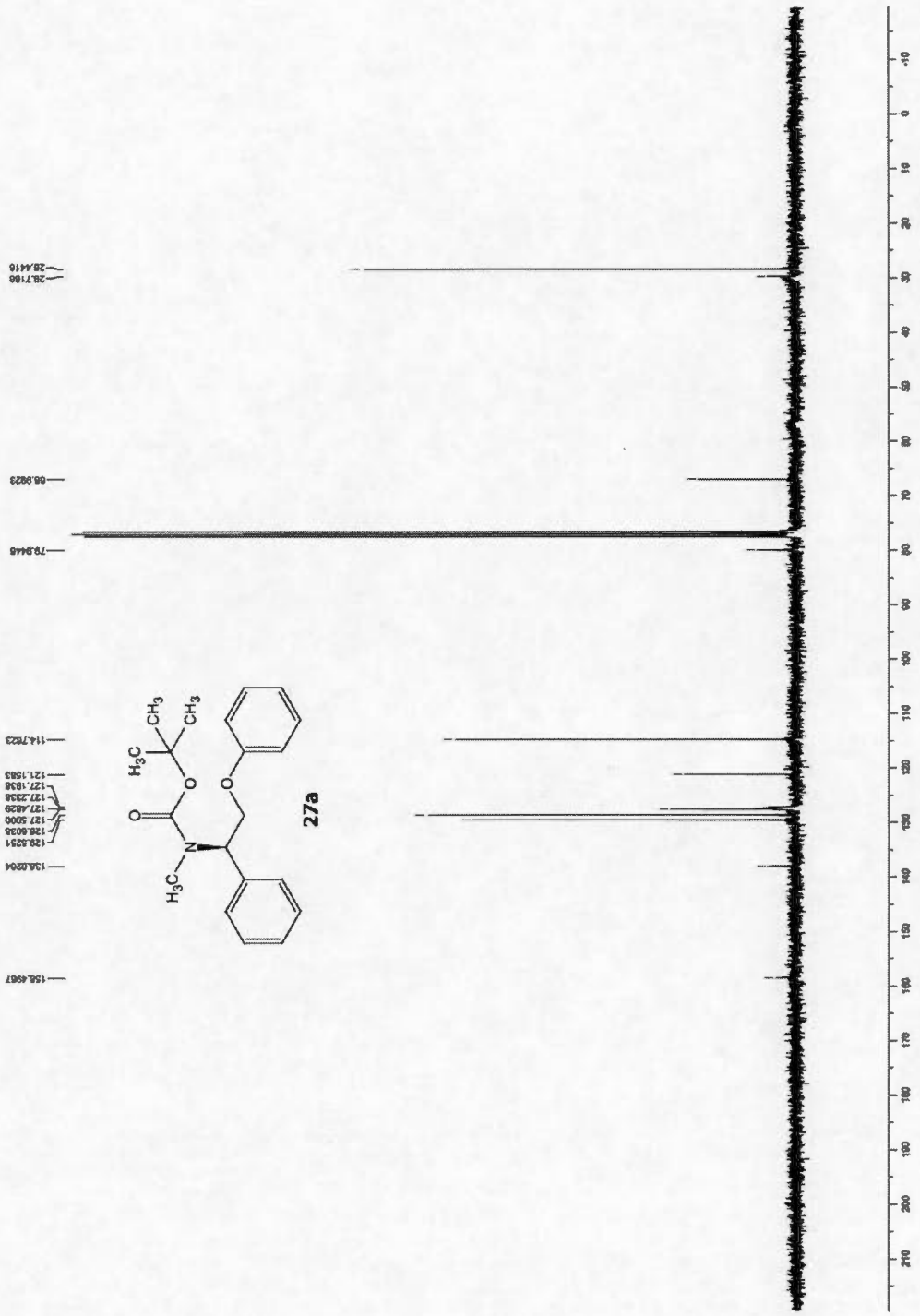

%Transmission
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
4000
3500
3000
2500
2000
1500
1000
Nombre d'onde (cm-1)
25a
3295,17
3061,26
3030,29
2924,58
2873,00
1633,89
1598,74
1579,27
1537,44
1491,98
1457,77
1387,86
1301,03
1239,43
1172,71
1152,27
1078,44
1041,54
909,18
882,20
753,38
690,94
520,00
513,69
511,88

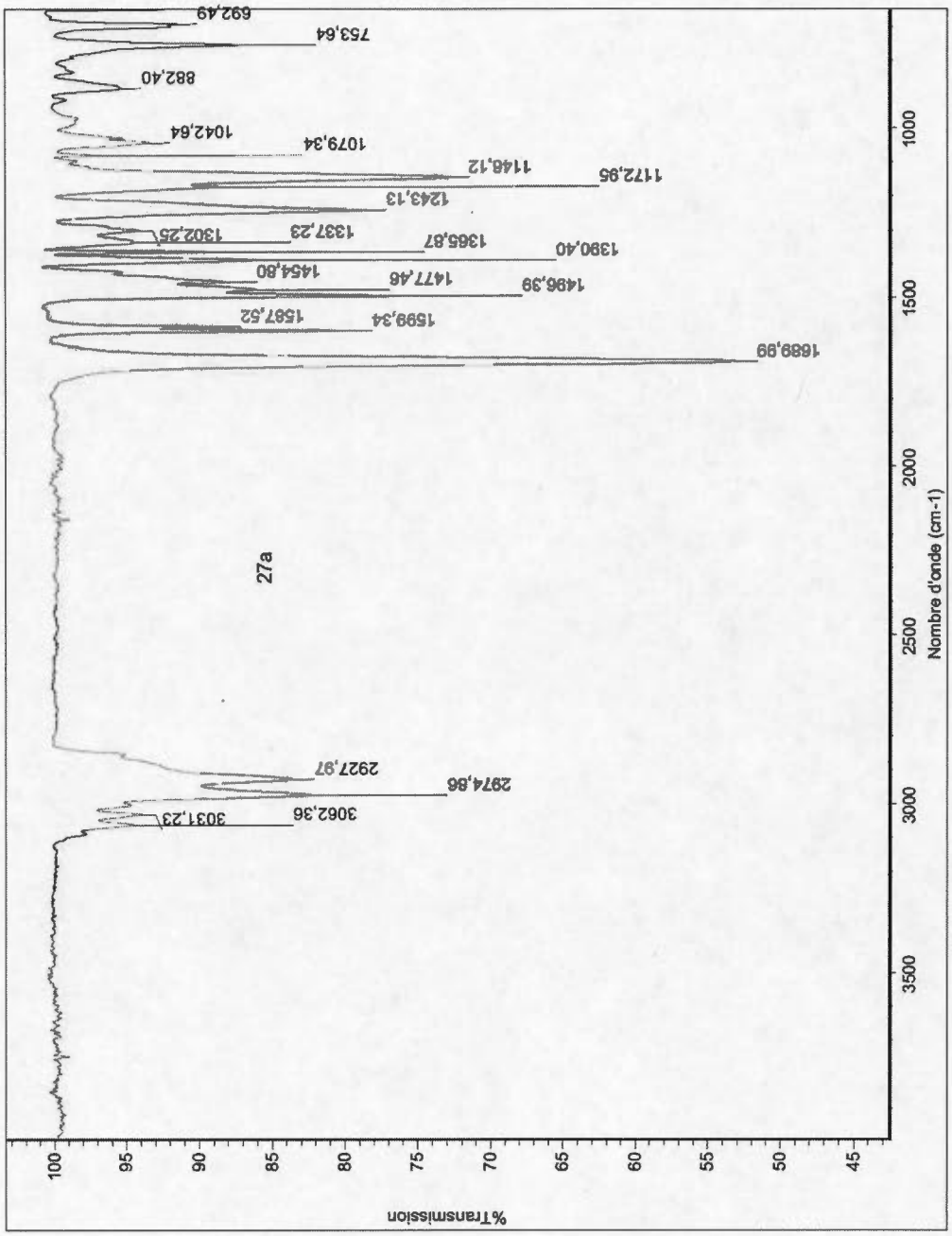

25b
NH
O


25b
NH
O
158.5857
140.5098
140.0701
128.4804
128.4250
128.1219
127.9114
127.8766
126.8252
121.0358
114.6840
72.7974
61.8048
51.3845


25b
%Transmission
Nombre d'onde (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
100
95
90
85
80
75
70
65
60
55
50
3304,03
3056,87
3022,64
2912,37
2847,73
1597,28
1494,19
1448,41
1322,93
1237,95
1144,22
1079,57
976,91
805,80
752,30


27a


28.4416
28.7186
68.8825
79.9446
114.7823
121.1583
127.1836
127.2336
127.4829
127.5900
128.6036
129.5251
136.0264
158.4567
27a


%Transmission
100
95
90
85
80
75
70
65
60
55
50
45
3500
3000
2500
2000
1500
1000
Nombre d'onde (cm-1)
27a
3062,36
3031,23
2974,86
2927,97
1689,99
1599,34
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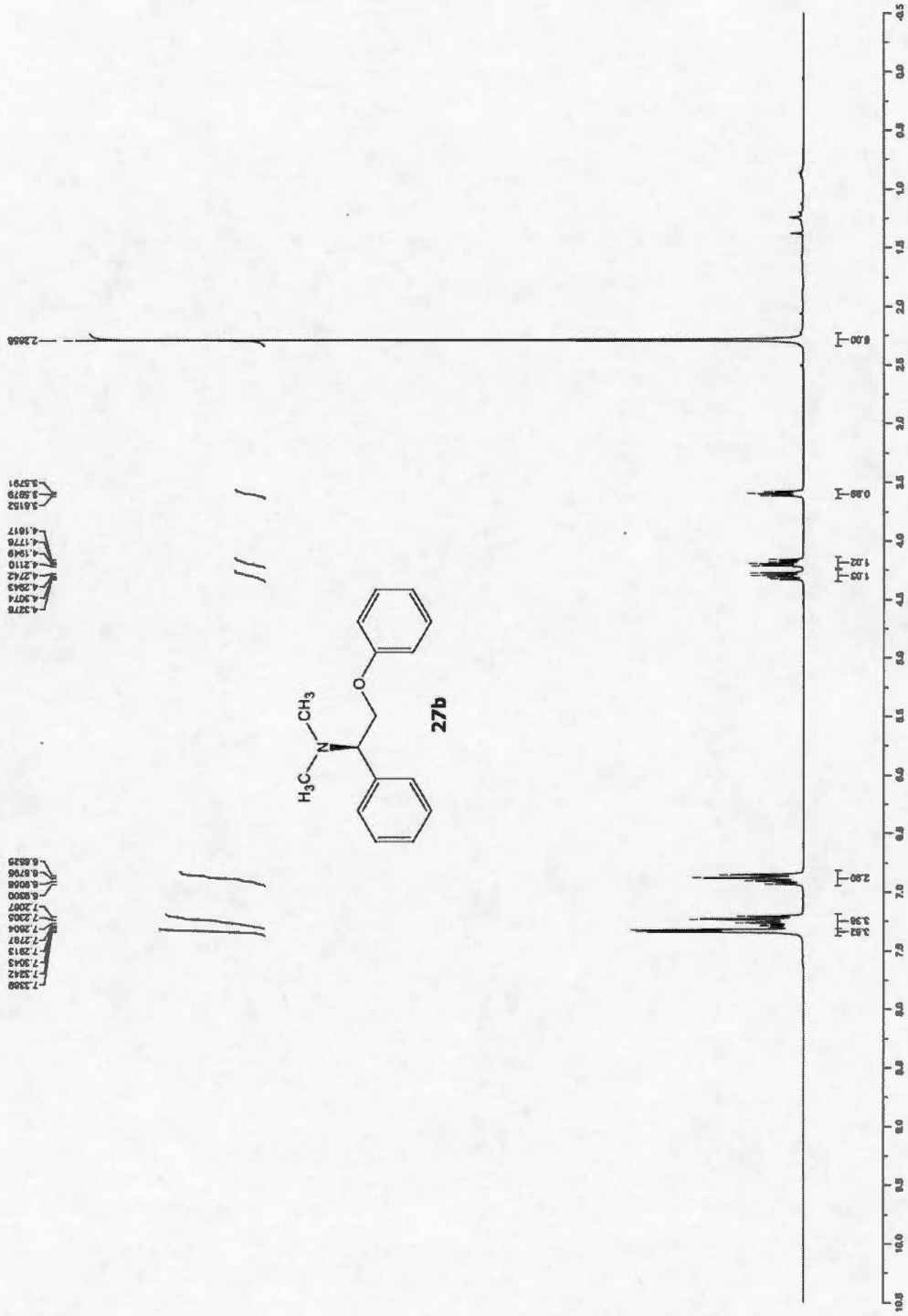
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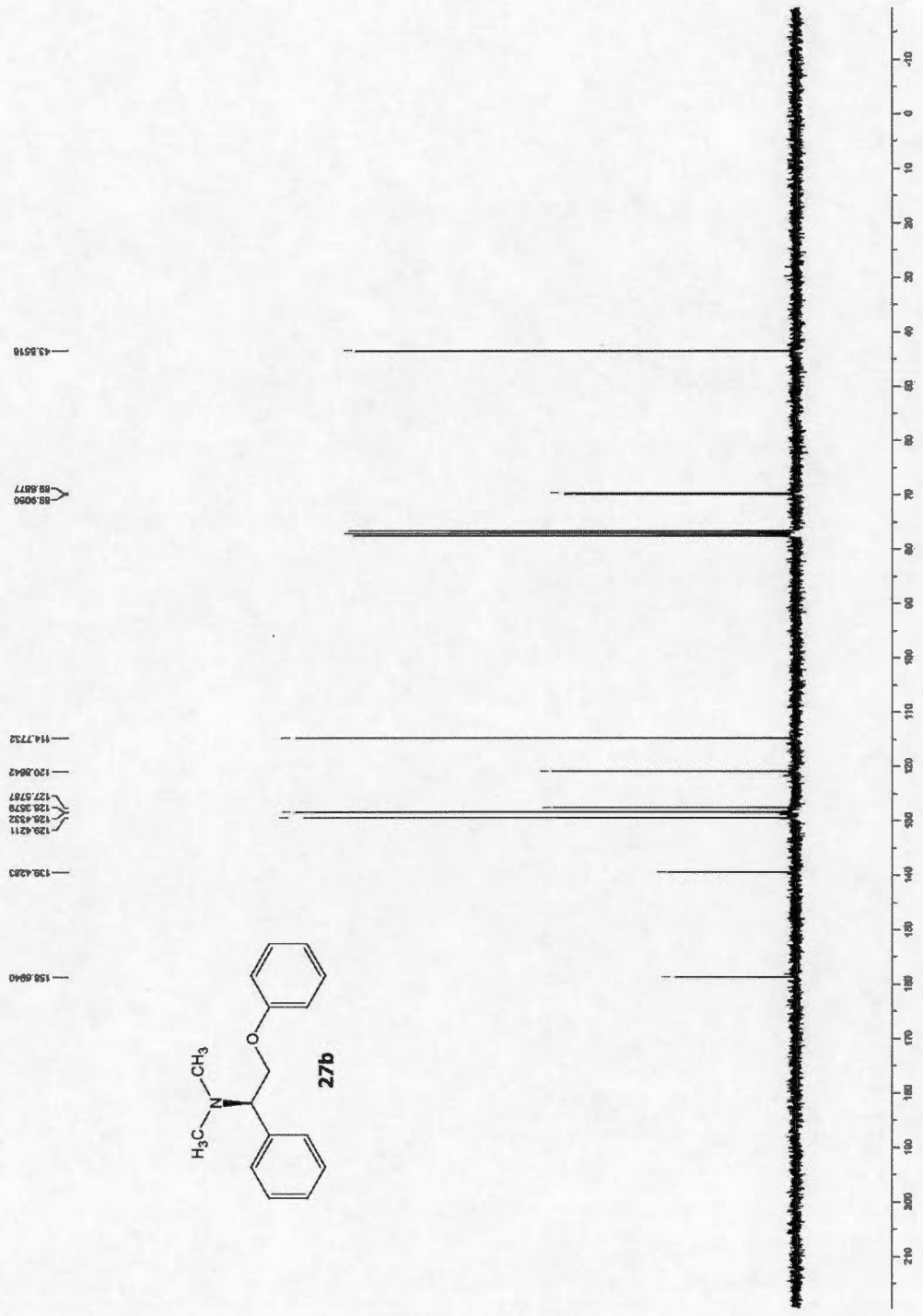
N
O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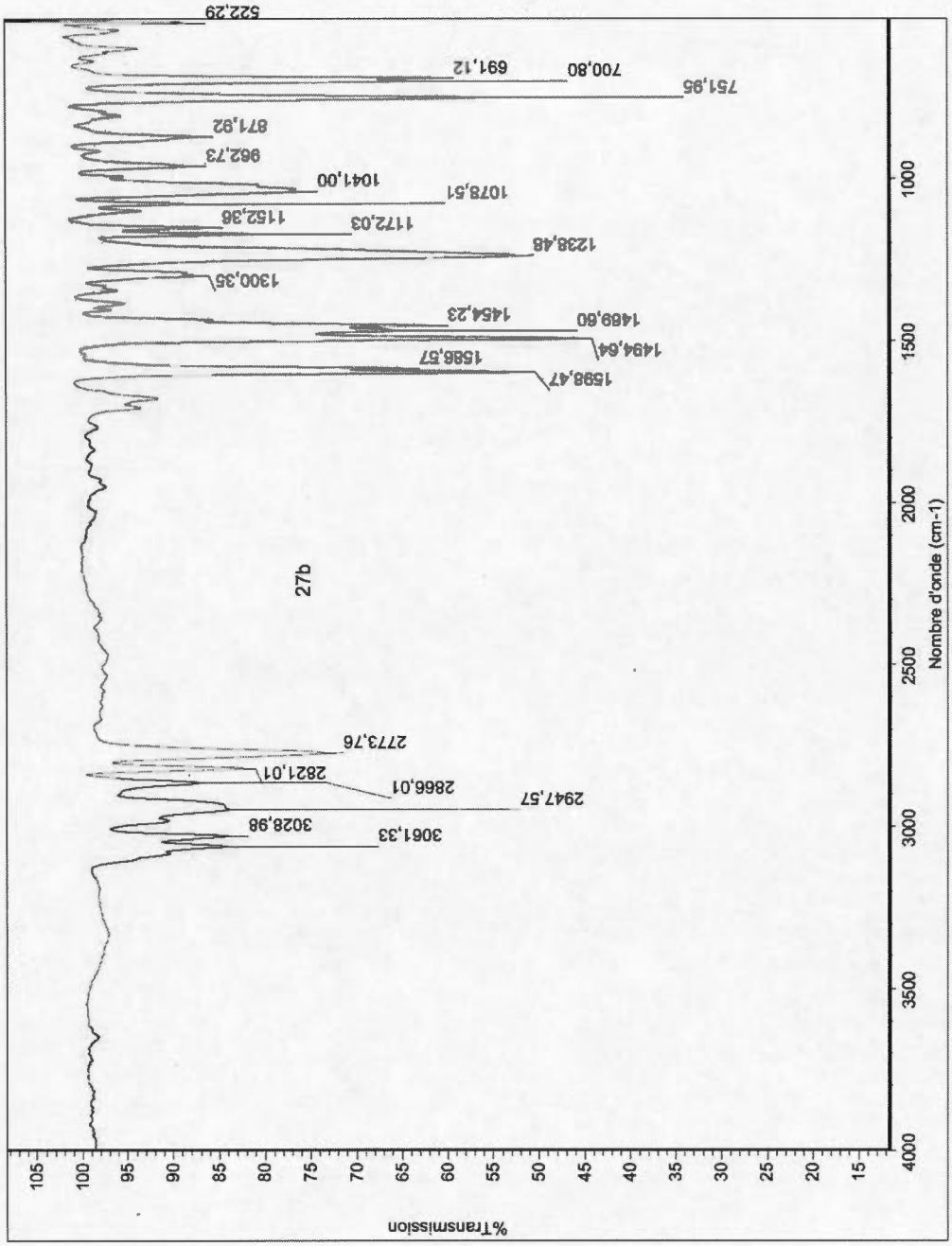
27b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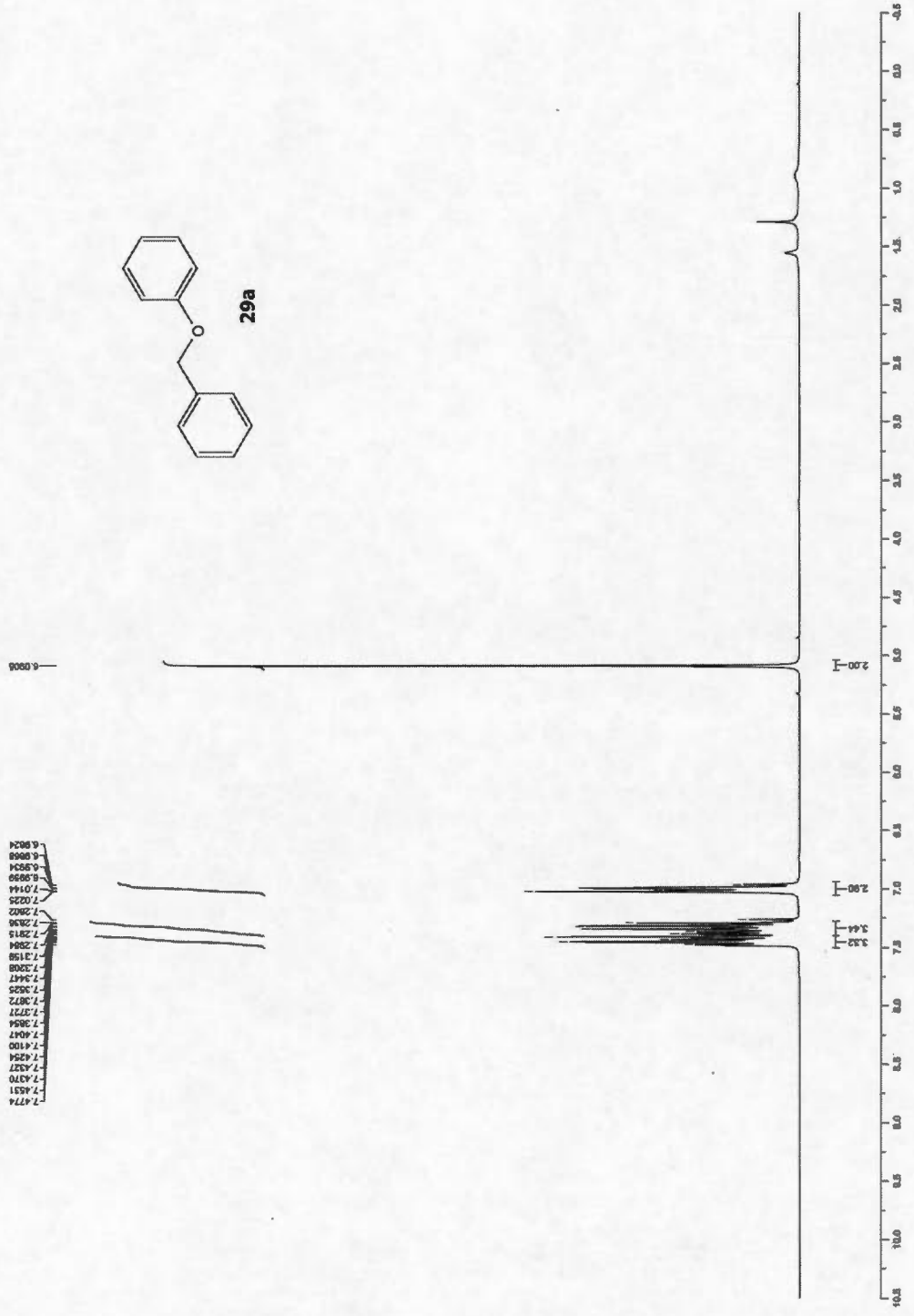
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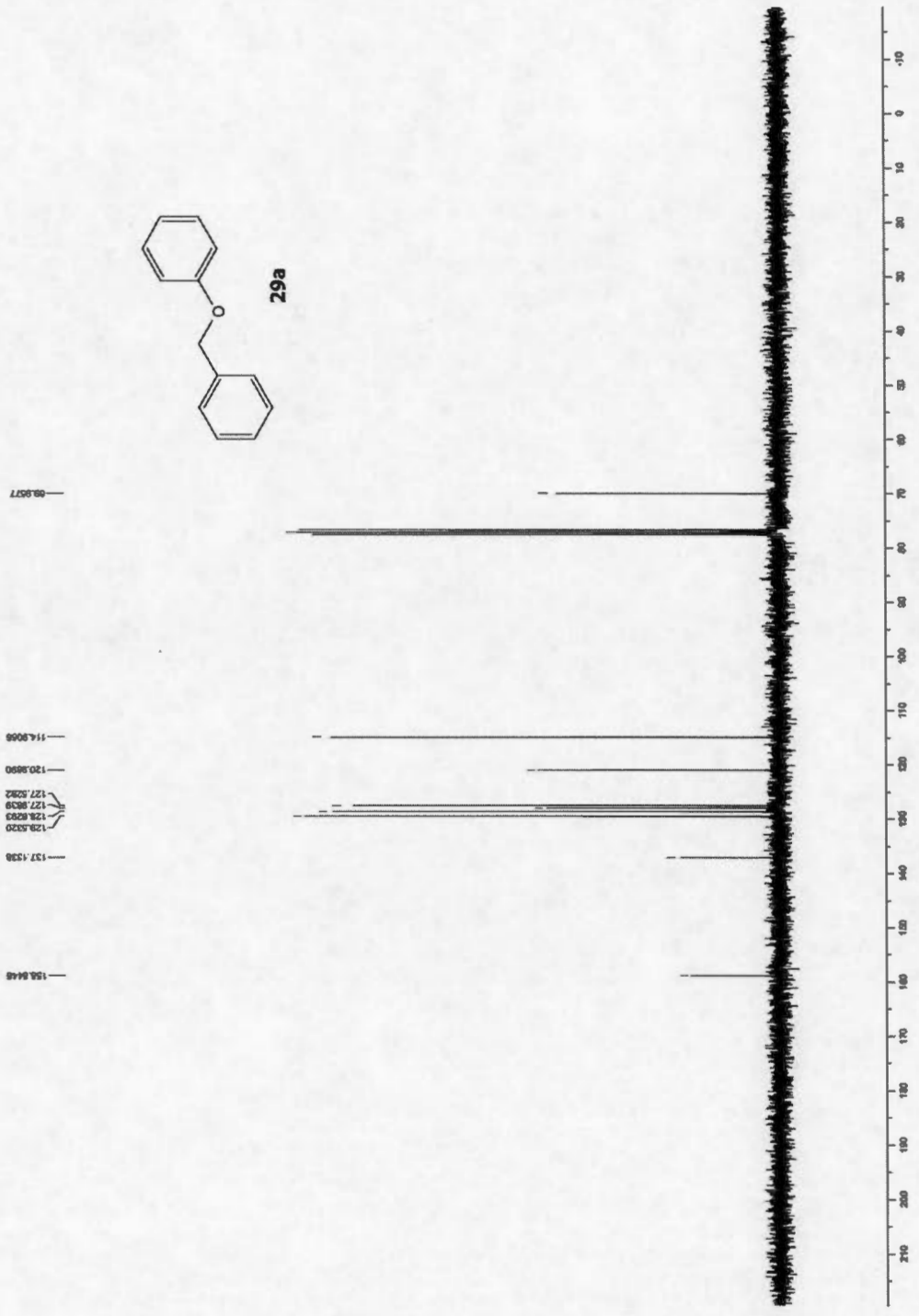
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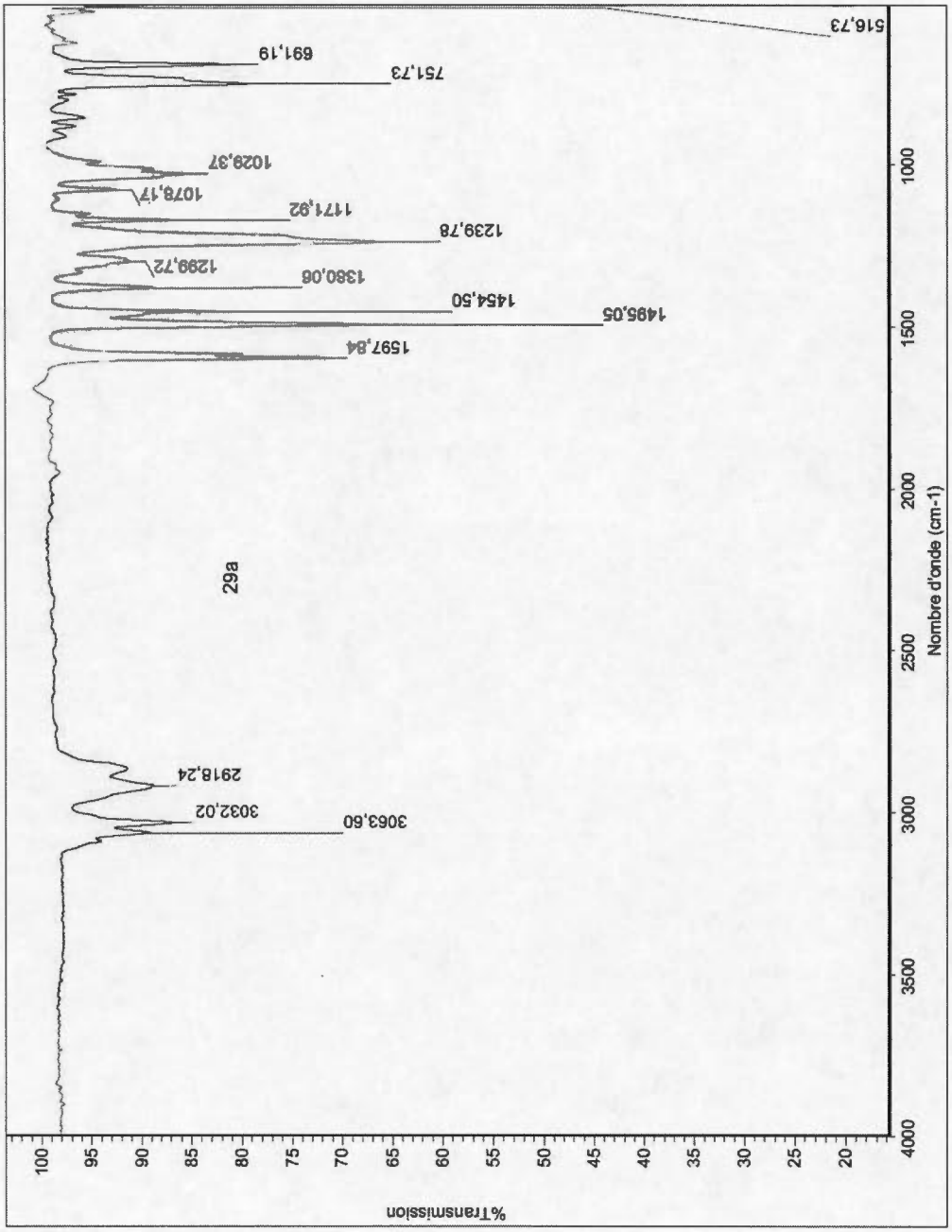
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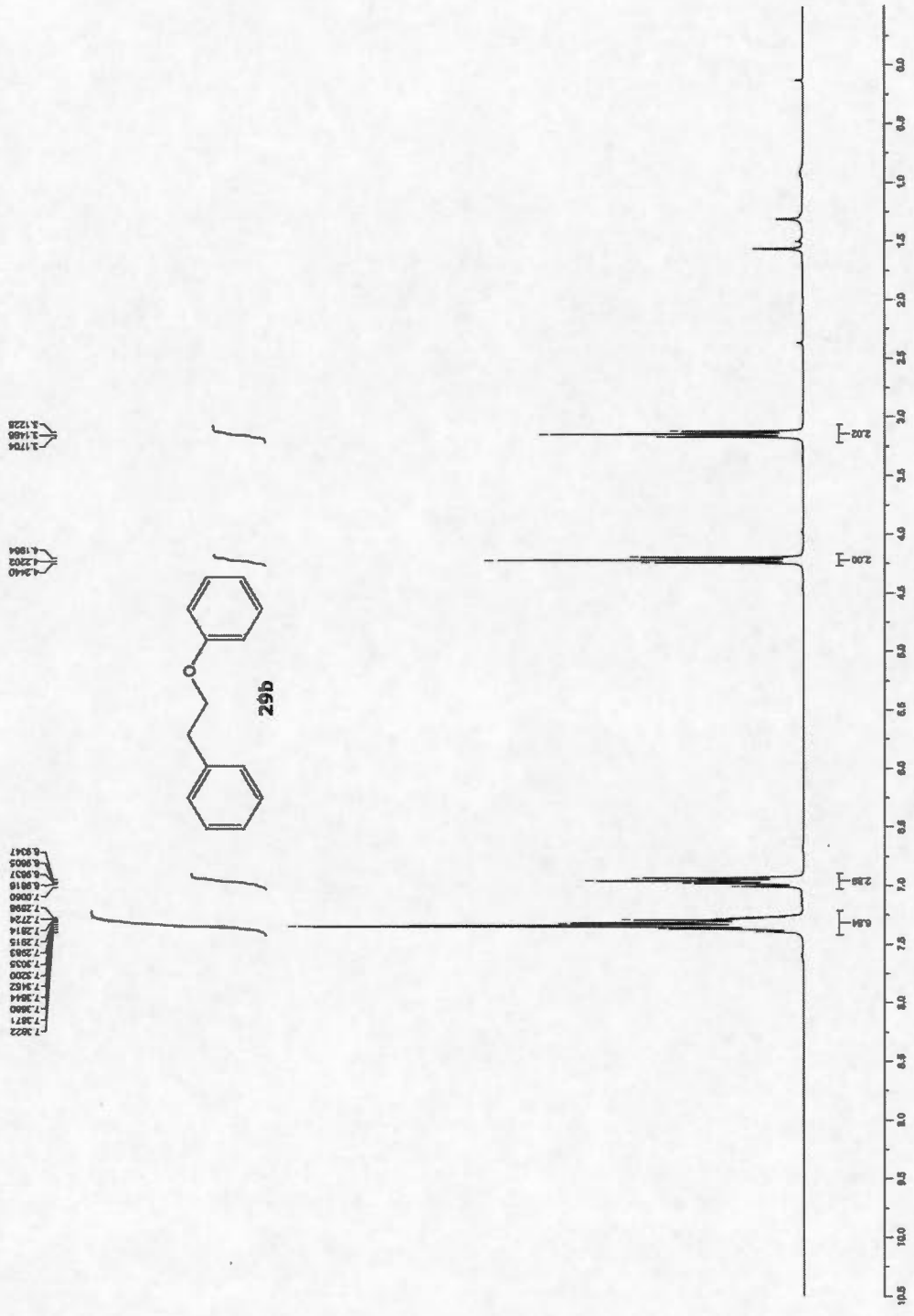
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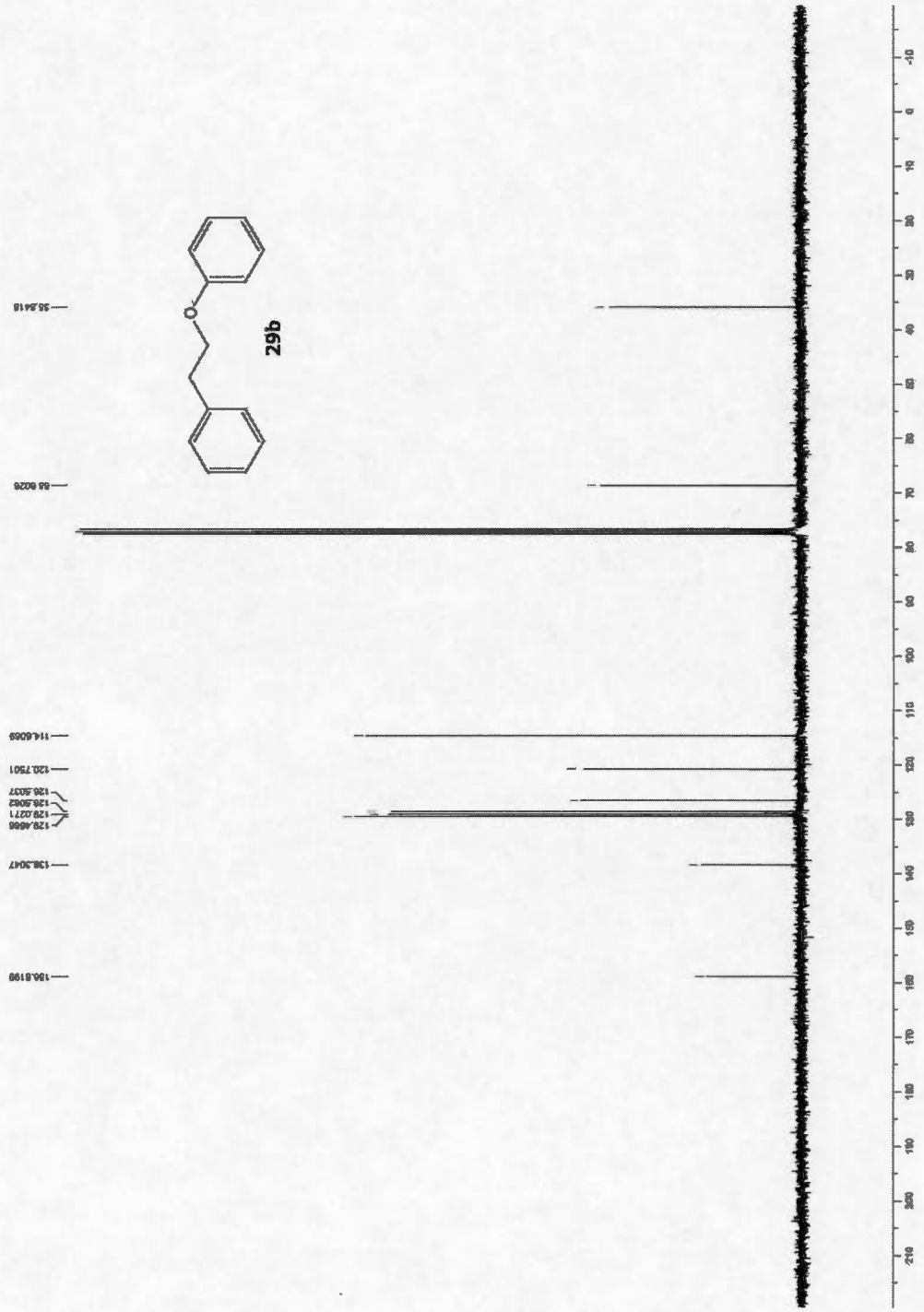
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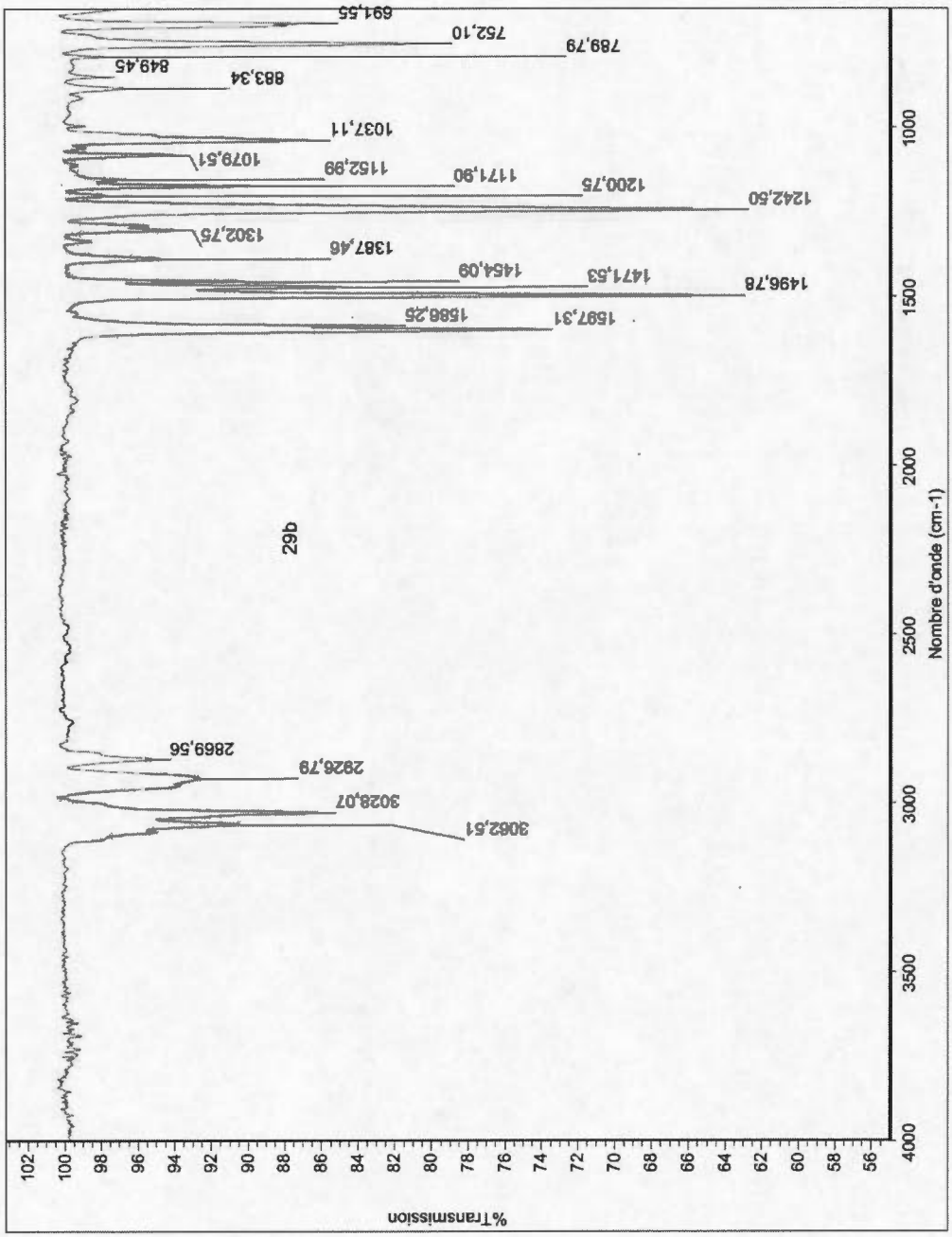
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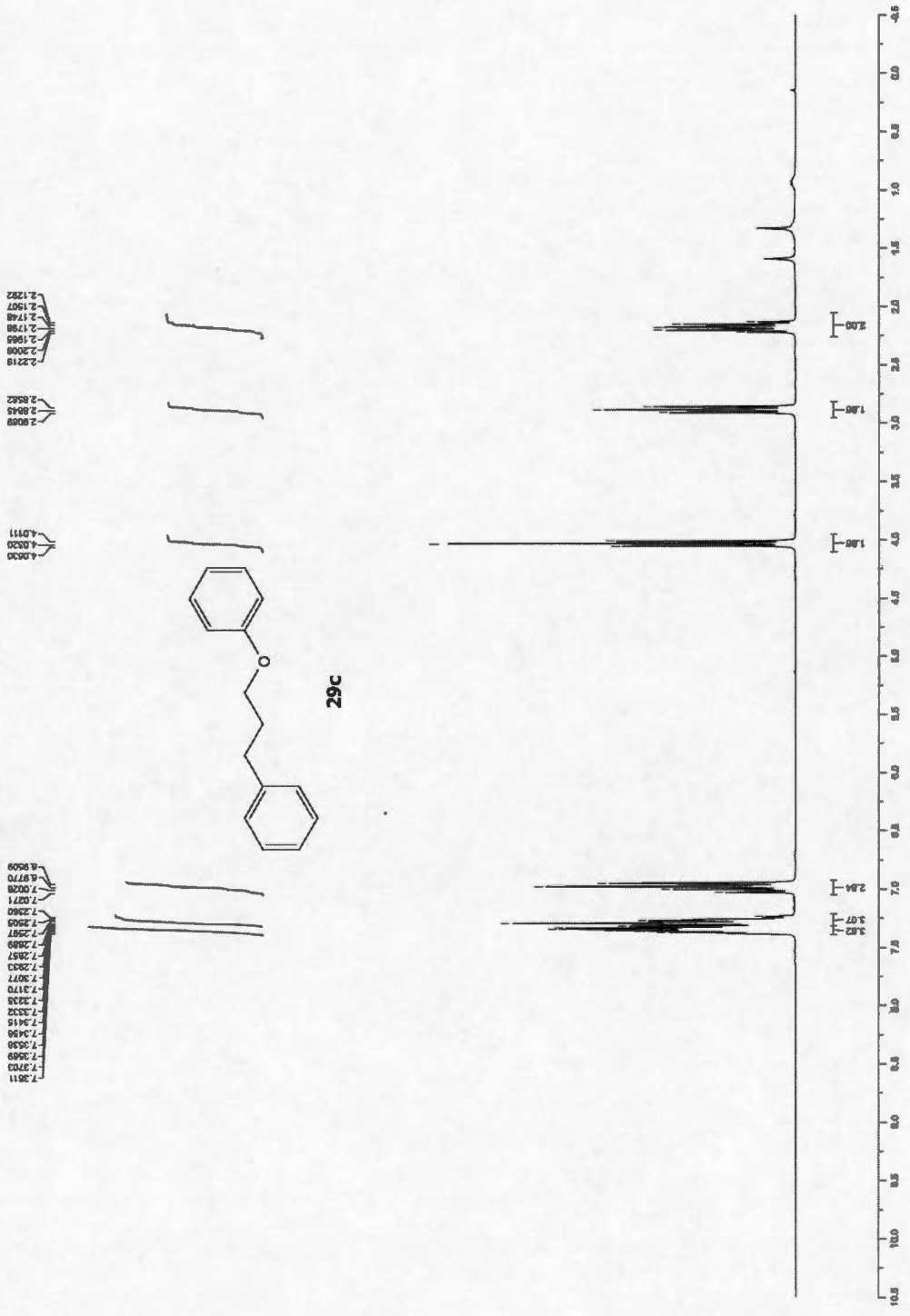
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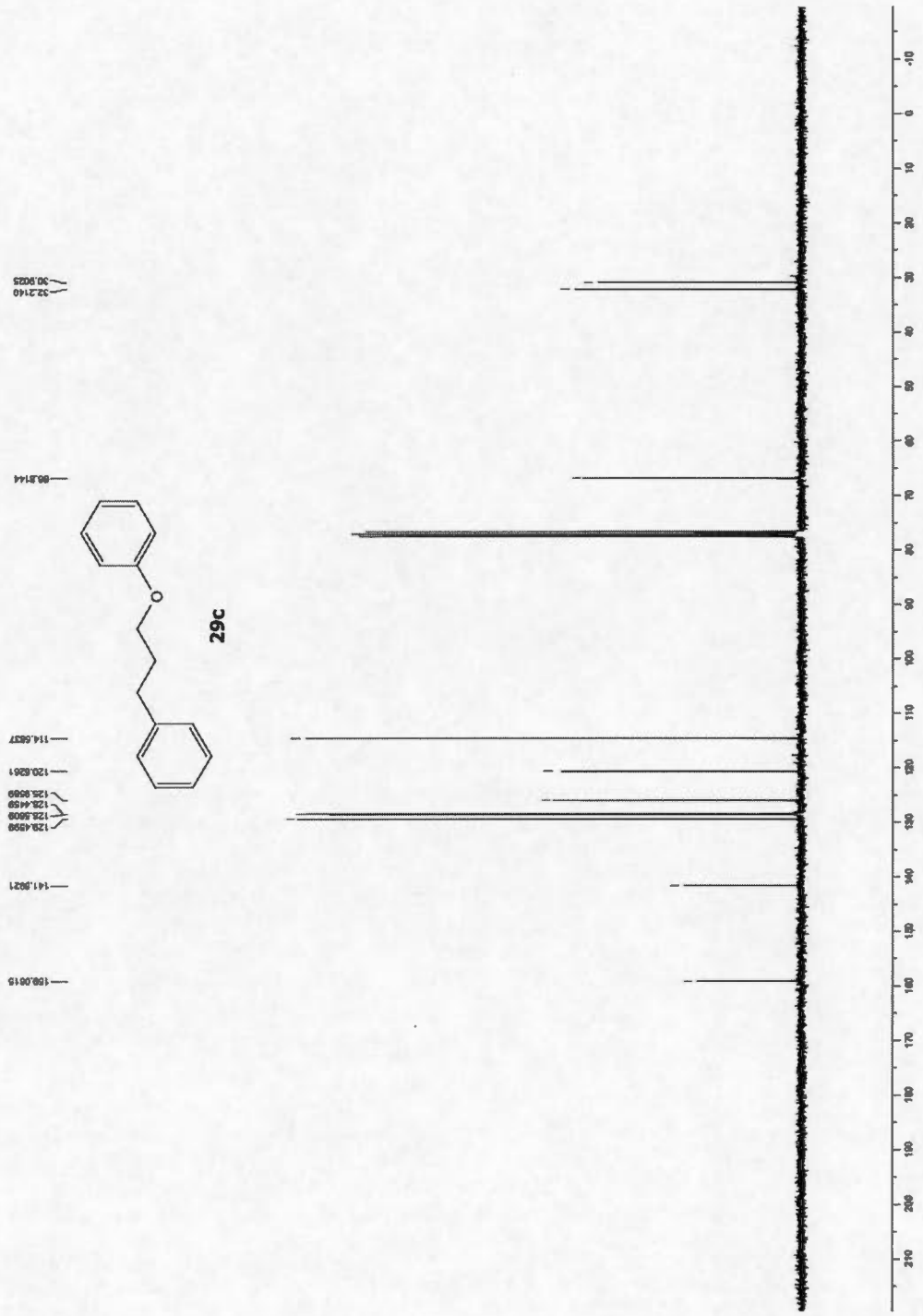
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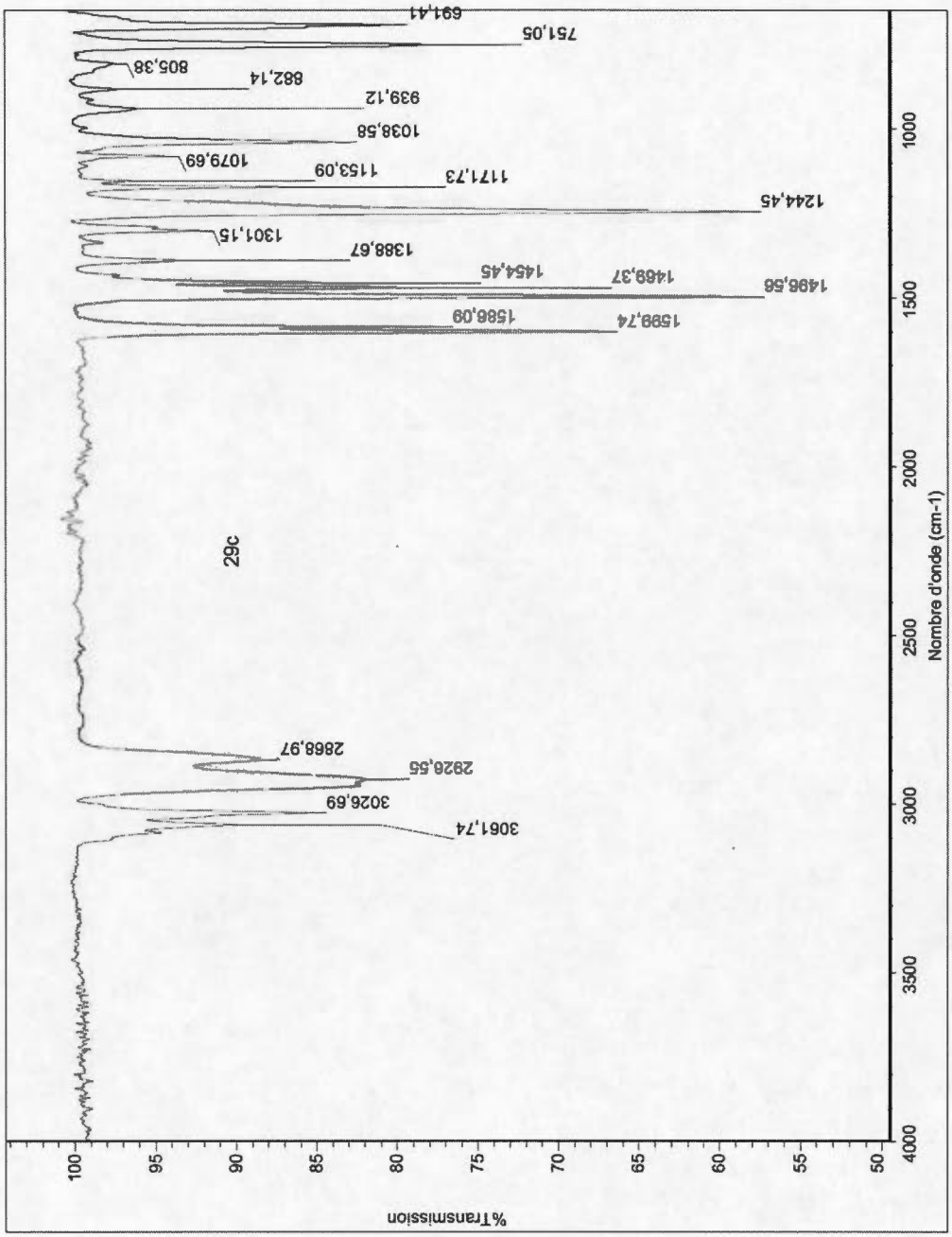
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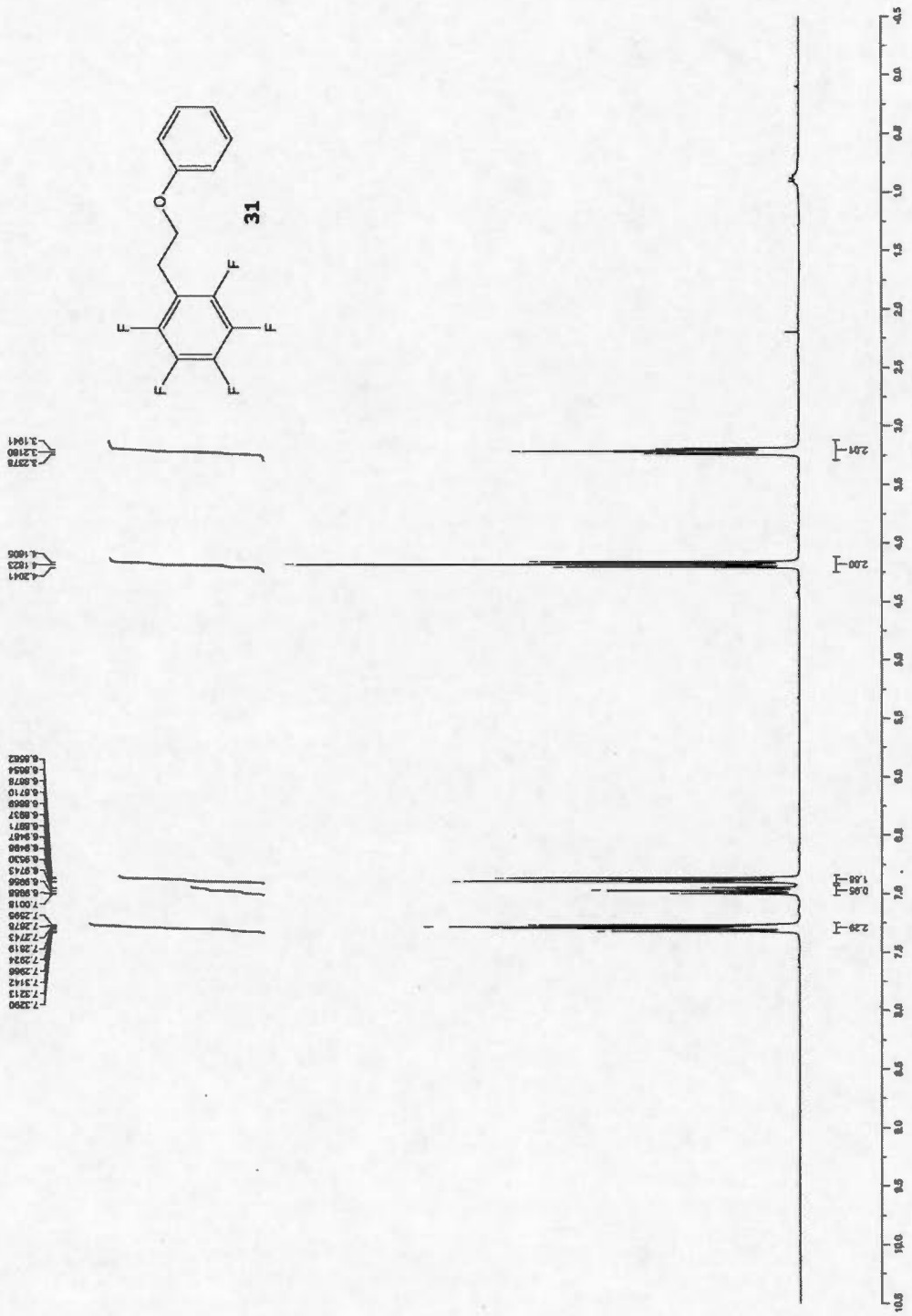
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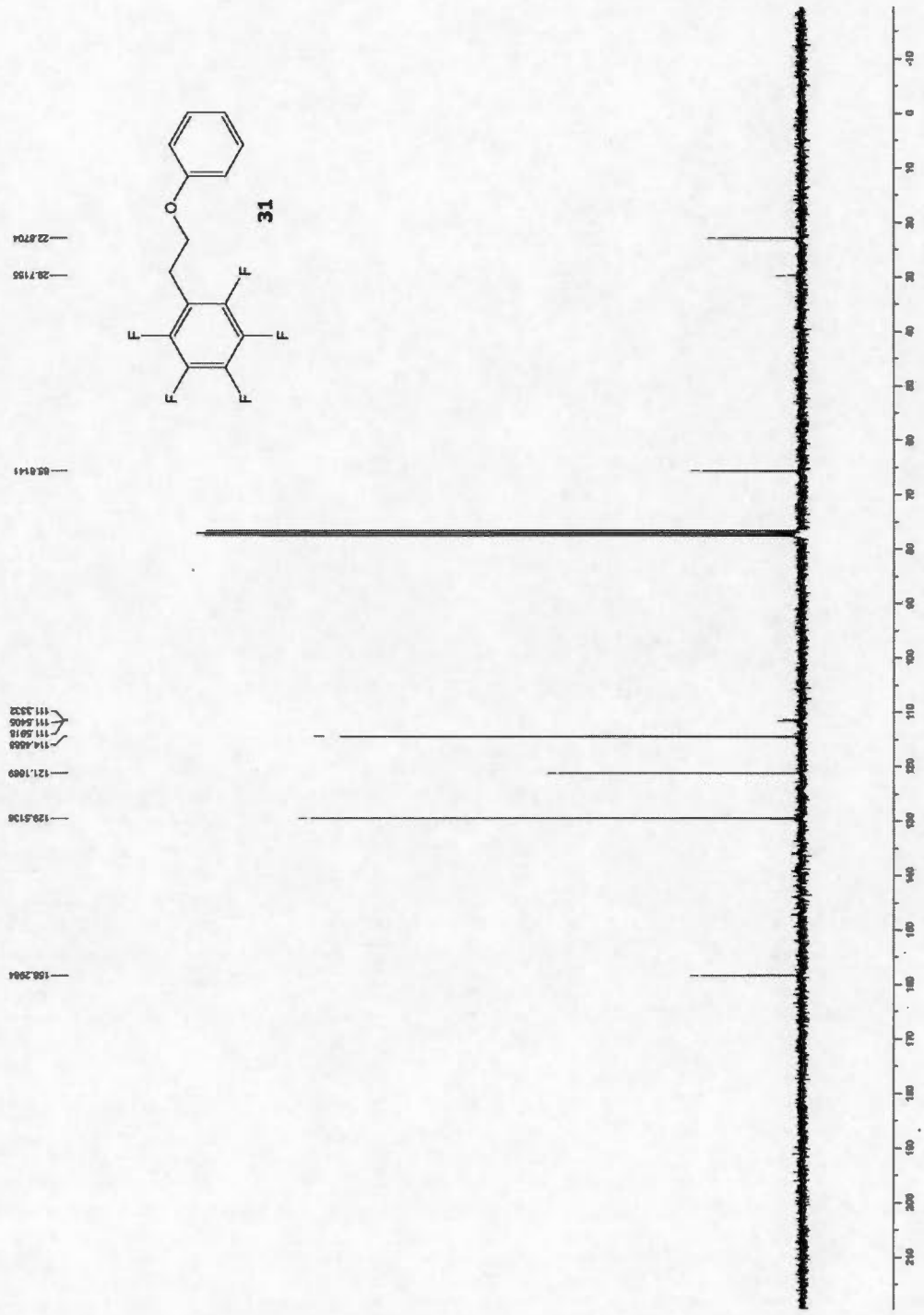
F
F
F
F
O


31
F
F
F
F
F
O
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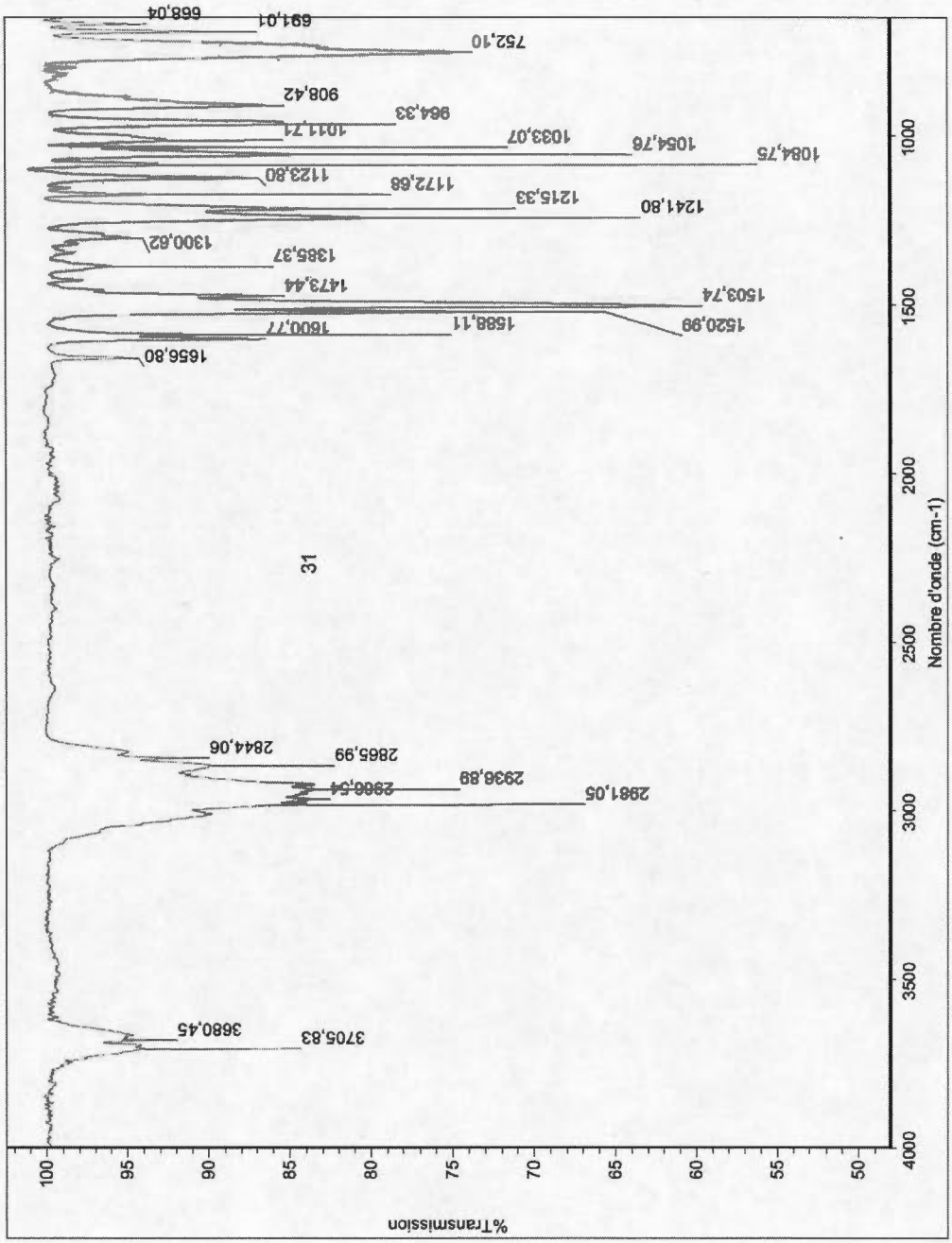
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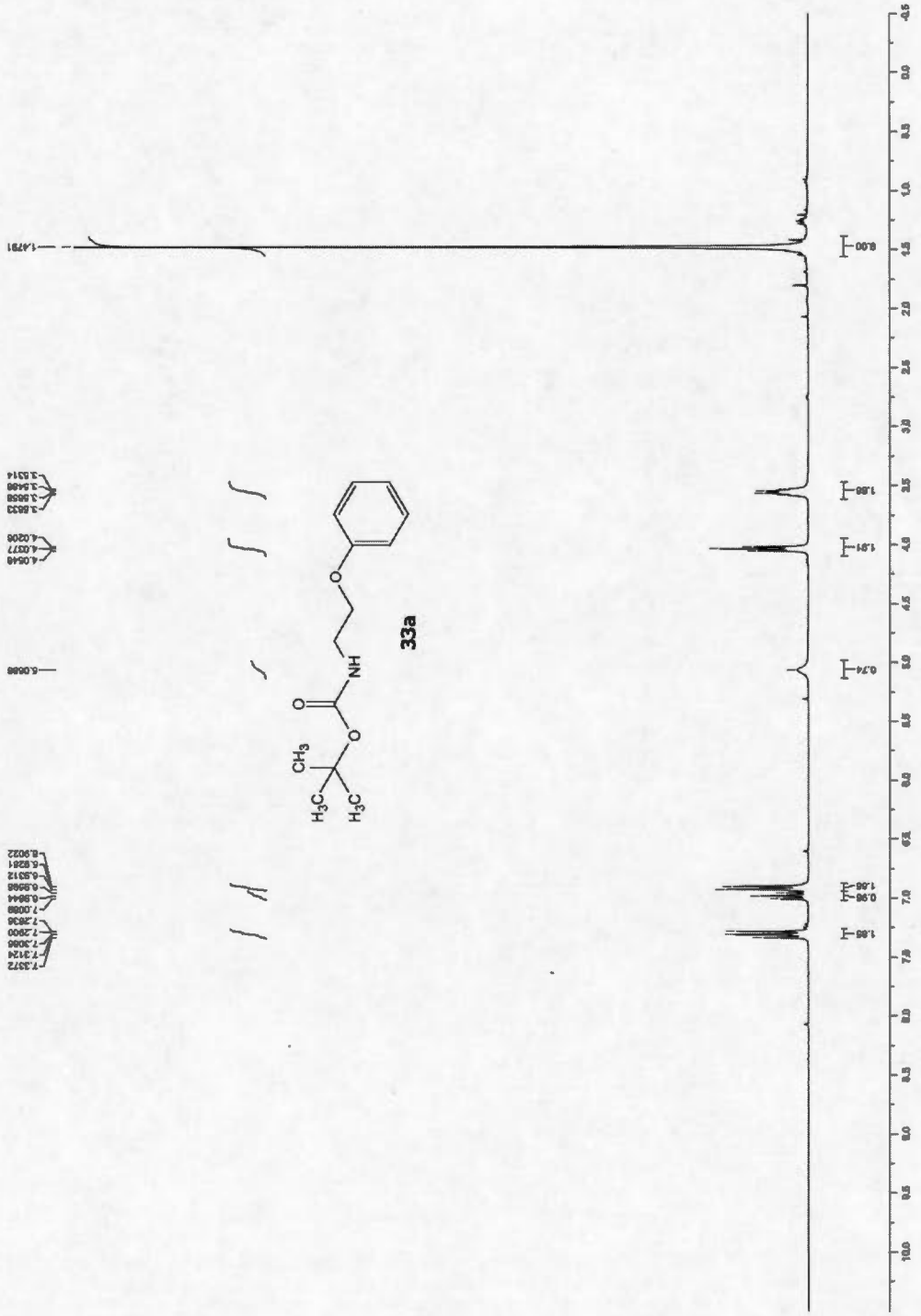
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O
O
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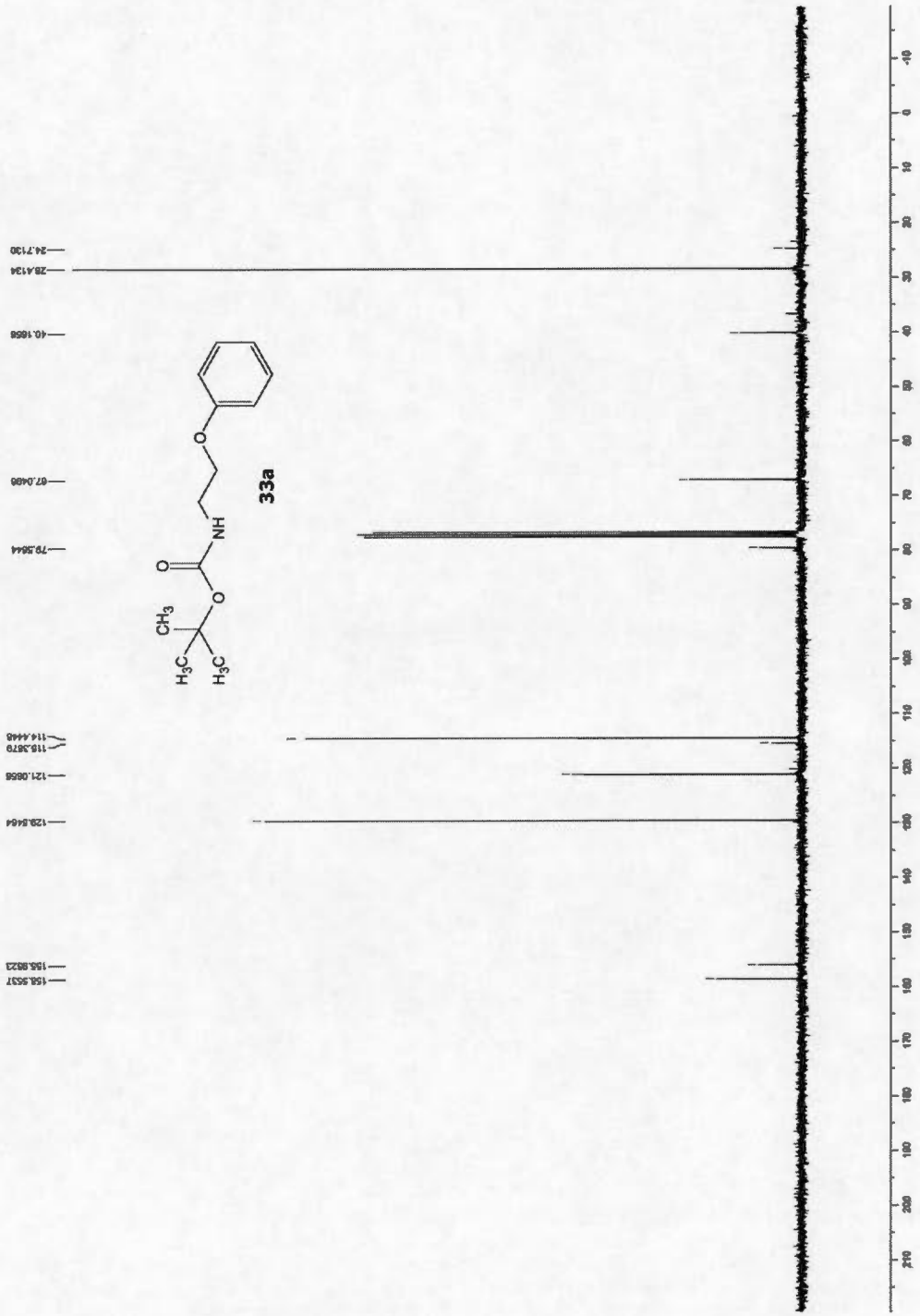
H3C
H3C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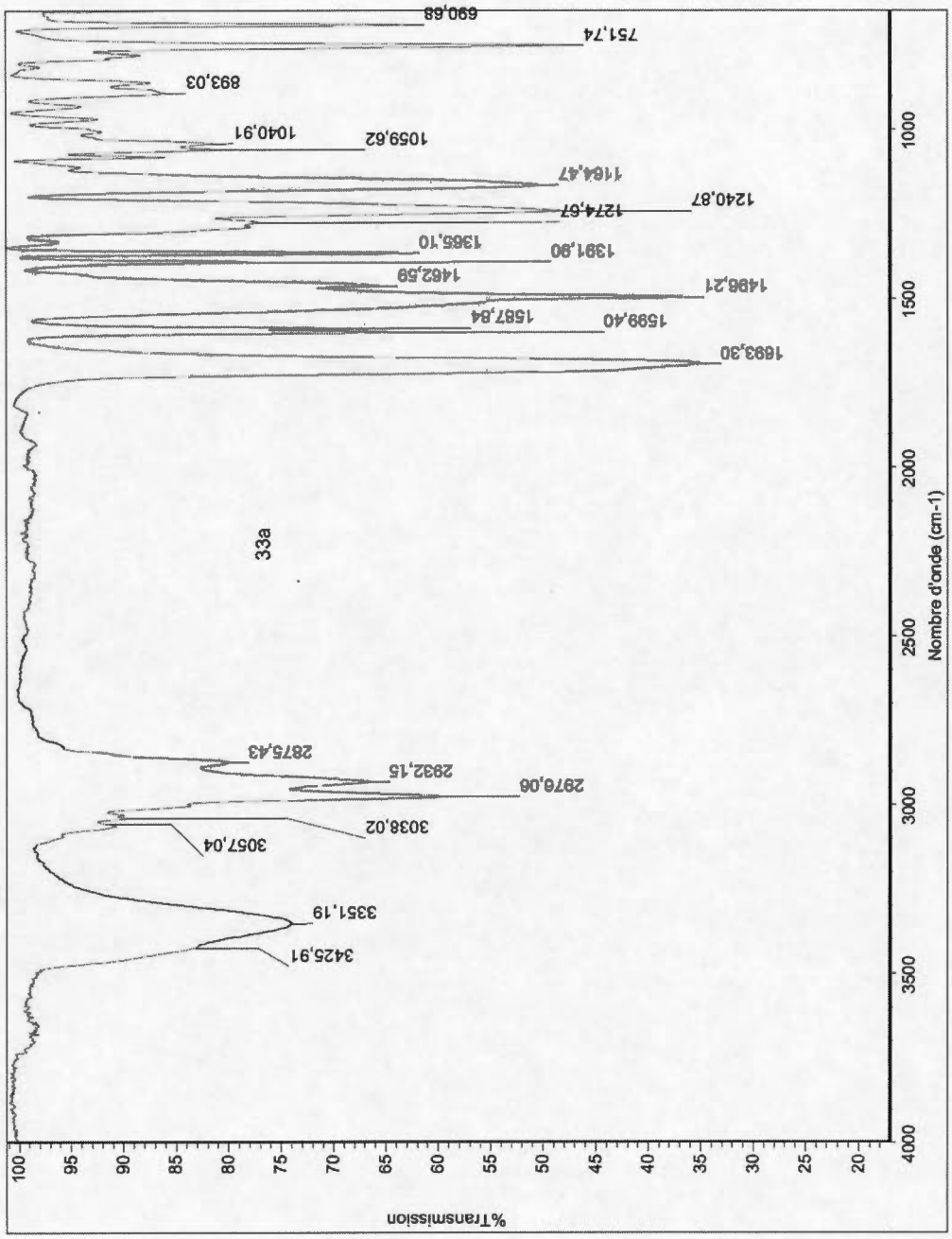
CH3
H3C
H3C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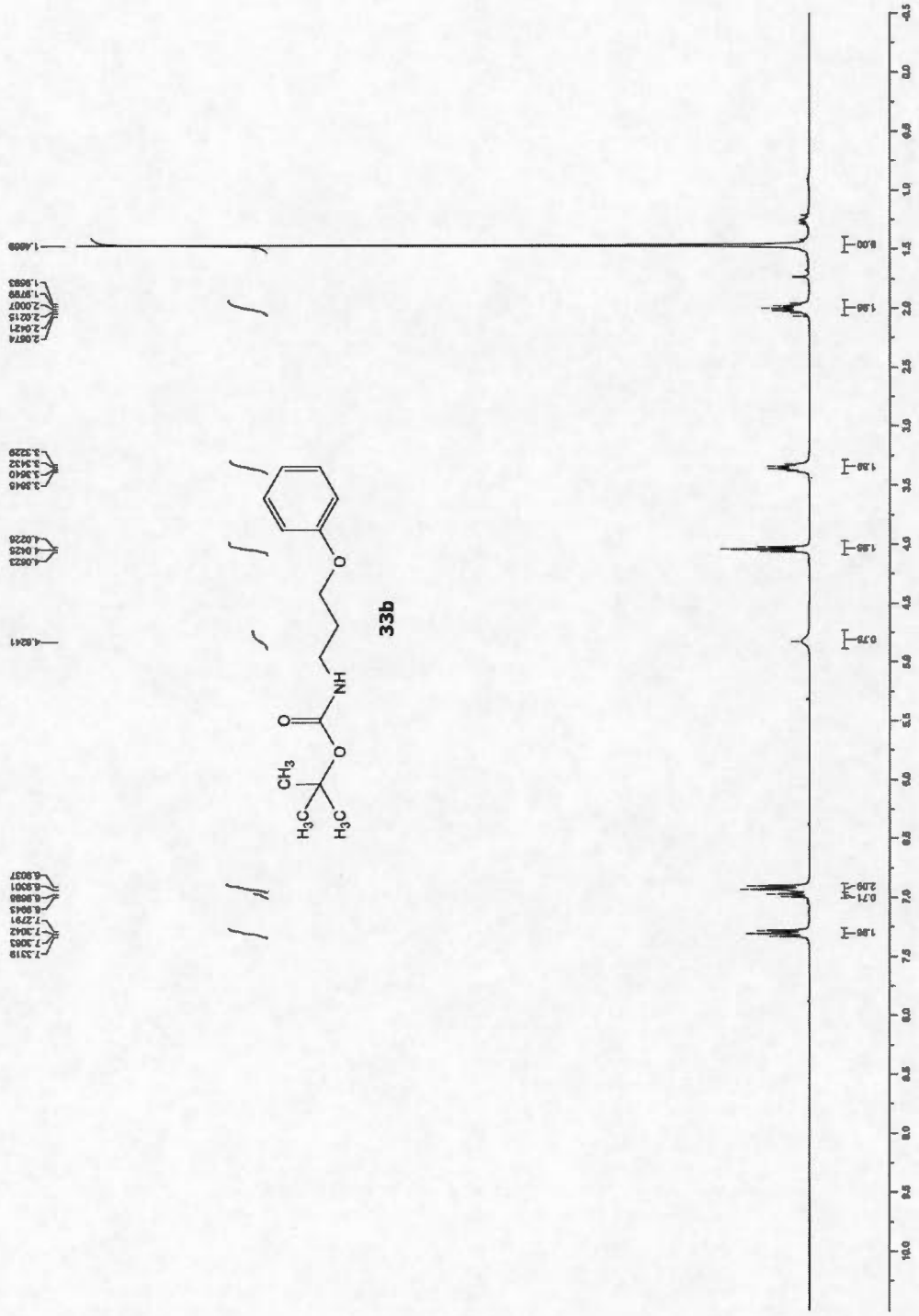
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CH3
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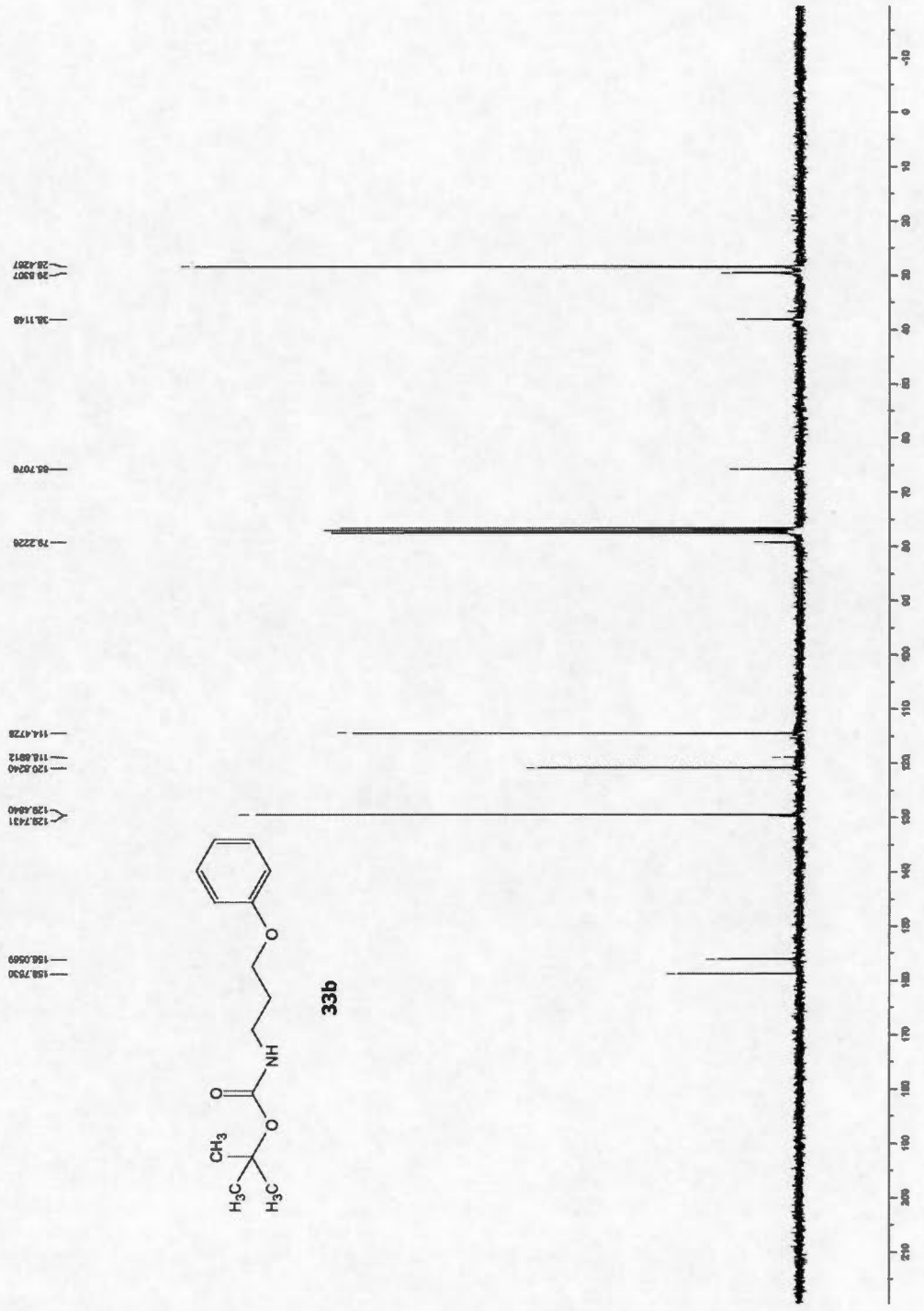
H3C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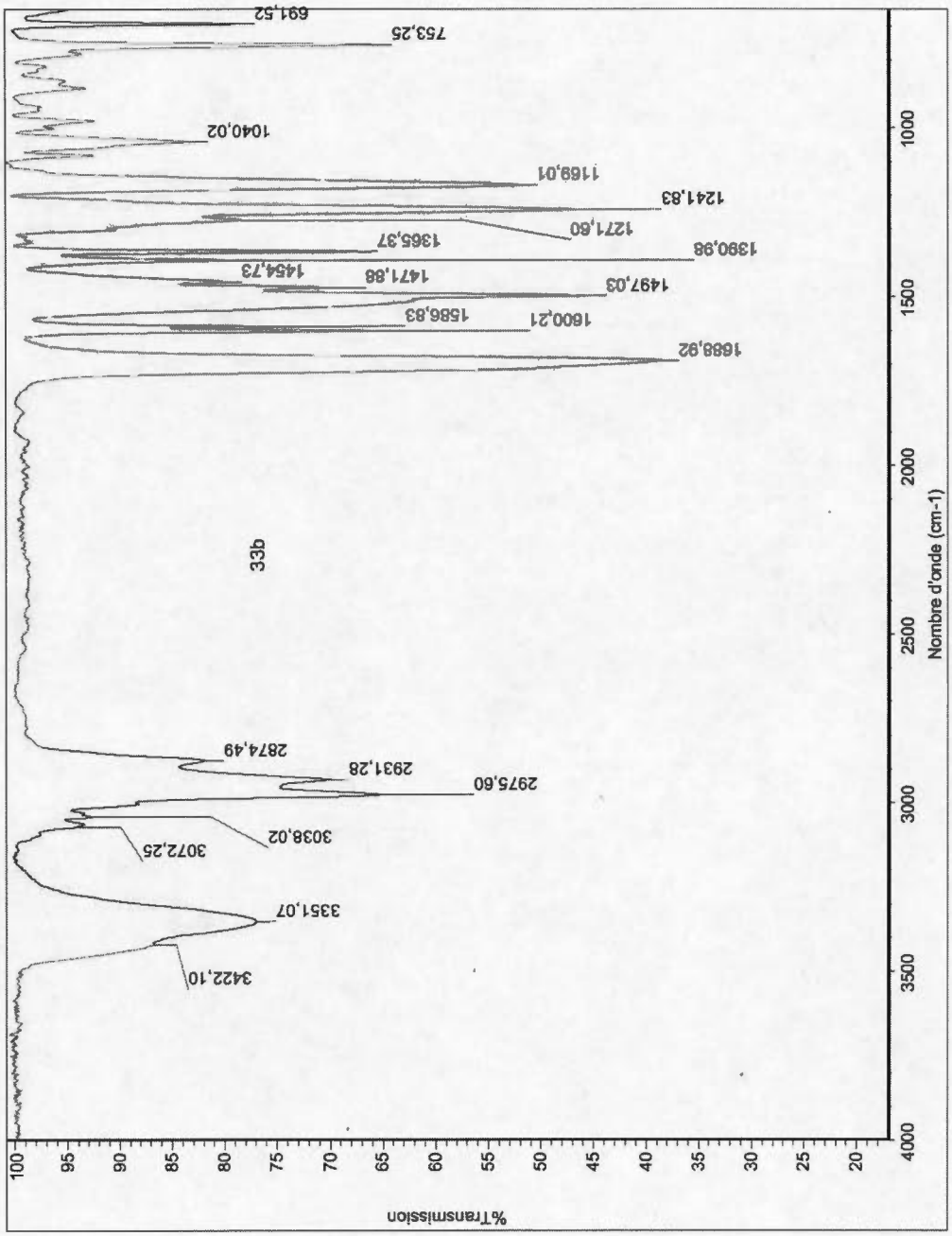
33b
O
NH
O
O
CH3
H3C
H3C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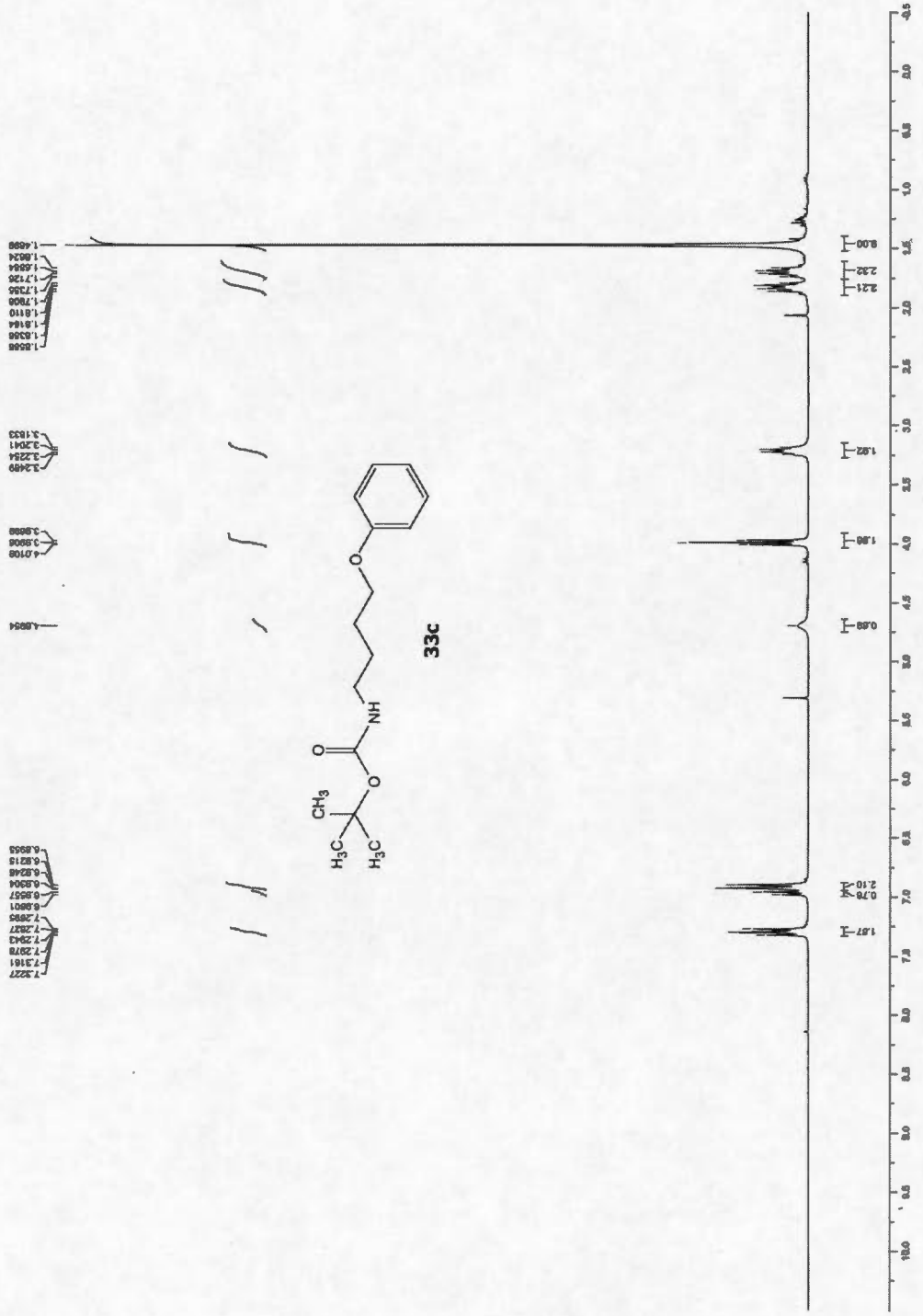
Nombre d'onde (cm-1)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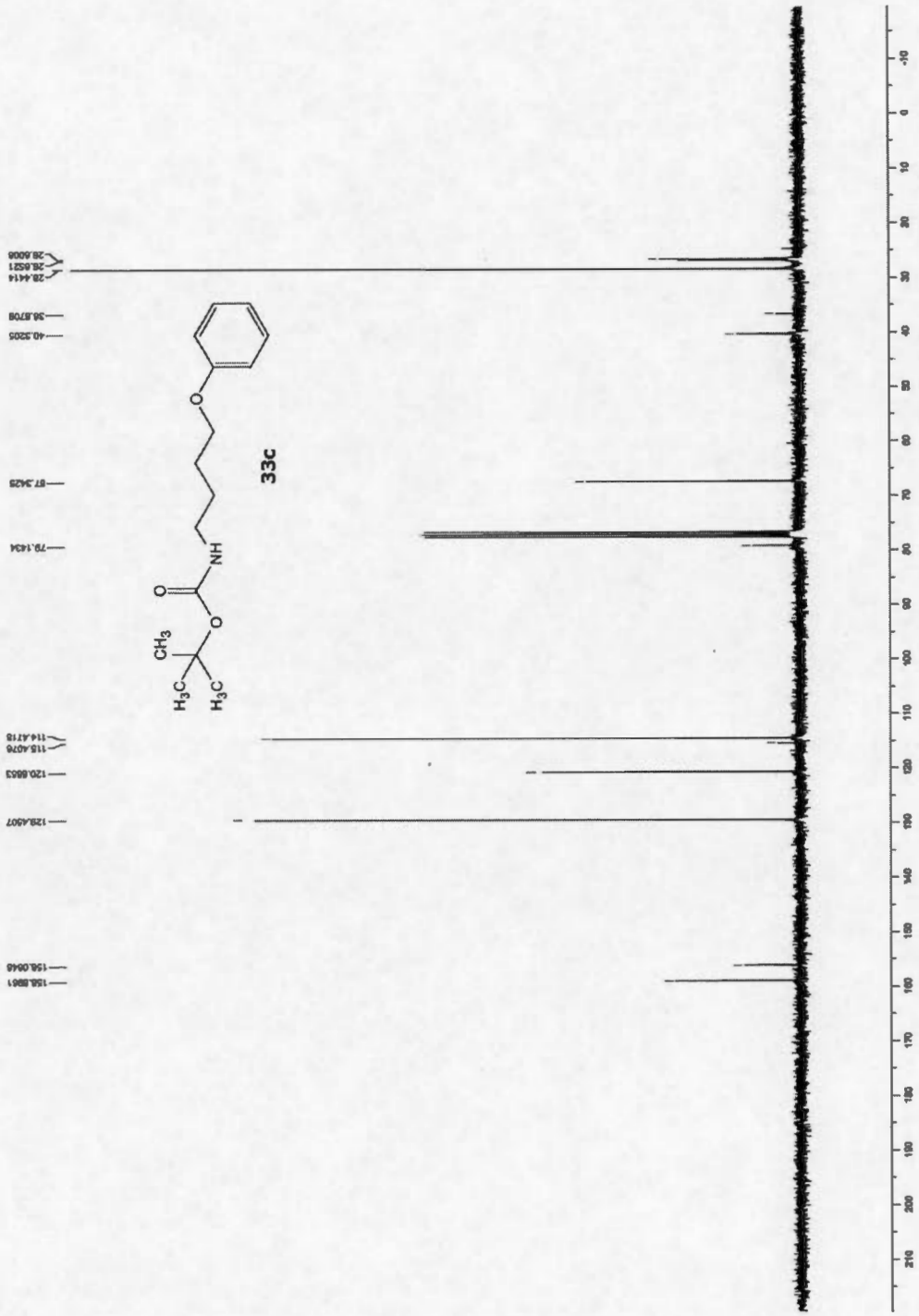
O
O
CH3
H3C
H3C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H3C
H3C
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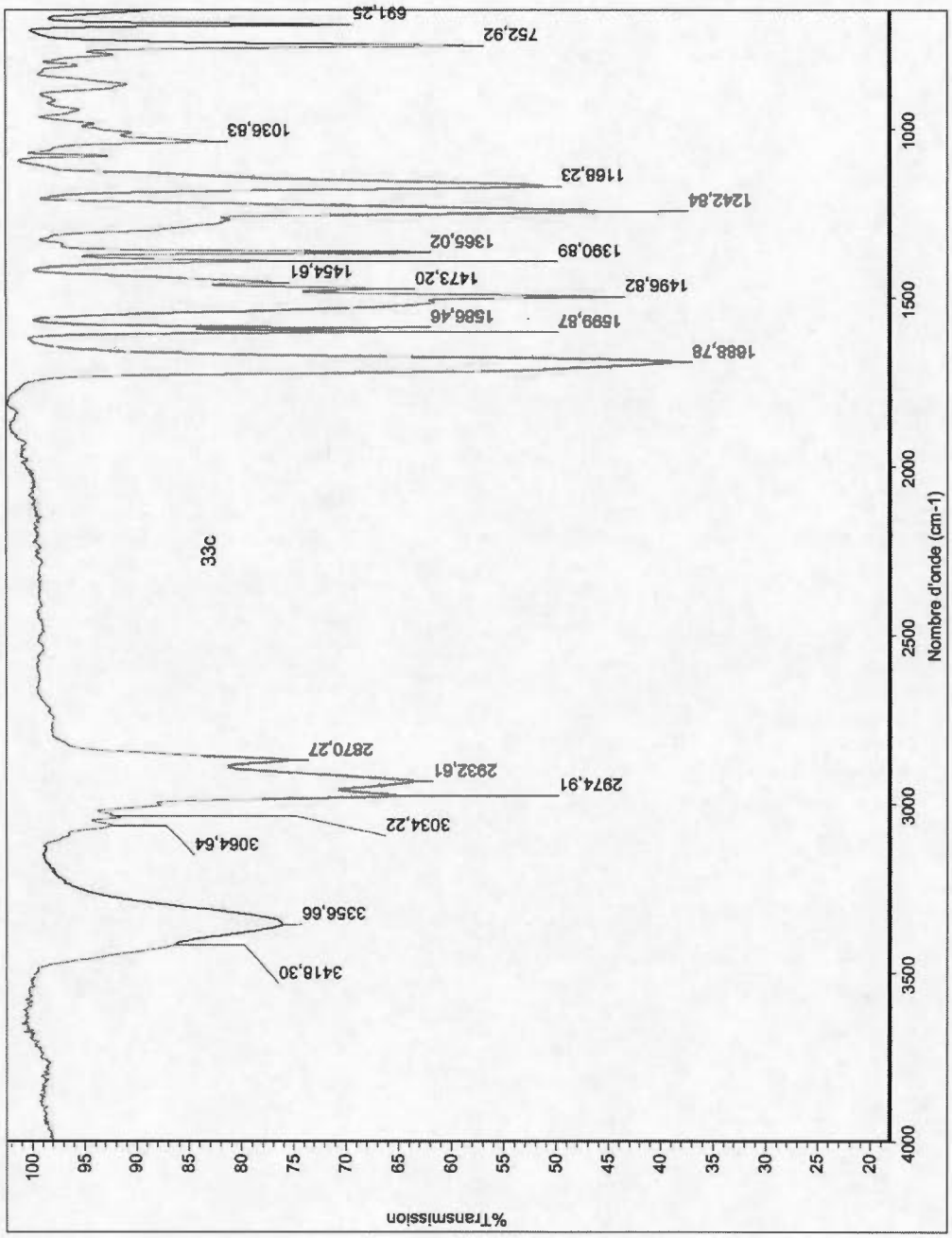
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752,92
691,25

f1 (ppm)
1.00
1.48
2.57
1.74
a
c
d
b
4.7759
5.0662
3.1986
2.9542

3.14
3.12
3.09
2.89
2.87
2.85
5.08
4.78
a
b
c
d
2.87
1.16
1.55
1.00
f1 (ppm)

ANNEXE I

"SYNTHESIS OF HIGHLY FUNCTIONNALIZED TRIARYLBISMUTHANES BY FUNCTIONNAL GROUP MANIPULATION AND USE IN *C*–, *N*–, AND *O*–, ARYLATION REACTIONS" ARTICLE

Article en cours de rédaction

Titre : Synthesis of Highly Functionnalized Triarylbismuthanes by Functionnal Group Manipulation and Use in *C*–, *N*–, and *O*–, Arylation Reactions

Auteurs : Pauline Petiot et Alexandre Gagnon*

Synthesis of Highly Functionalized Triarylbismuthanes by Functional Group Manipulation and use in *C*–, *N*–, and *O*–Arylation Reactions

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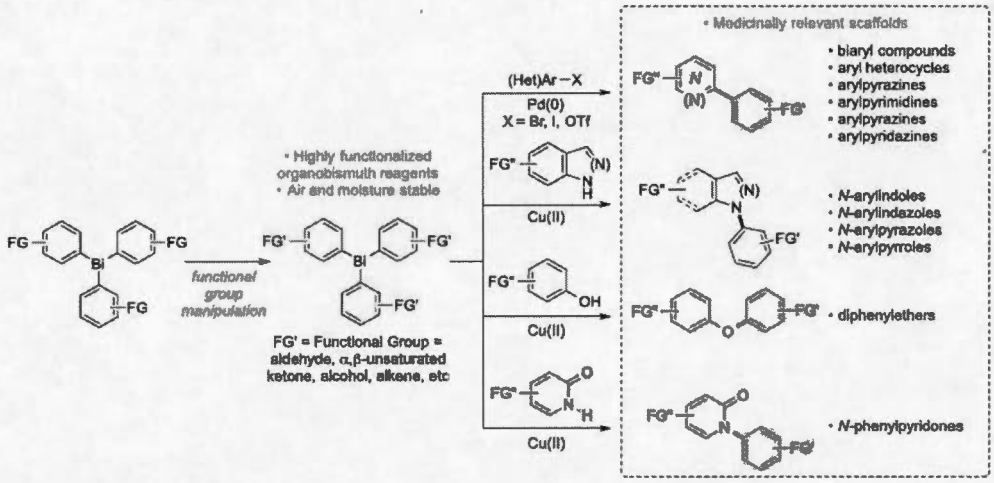
[b] Centre in Green Chemistry and Catalysis



ABSTRACT

Organobismuthanes are an attractive class of organometallic reagents that can be accessed from inexpensive and non toxic bismuth salts. Arylbismuthanes are particularly interesting since they are air and moisture stable and since they show high functional group tolerance. We report herein our detailed study on the preparation of highly functionalized triarylbismuth reagents by functional group manipulation and their use in palladium and copper-catalyzed *C*–, *N*–, and *O*–arylation reactions.

INTRODUCTION

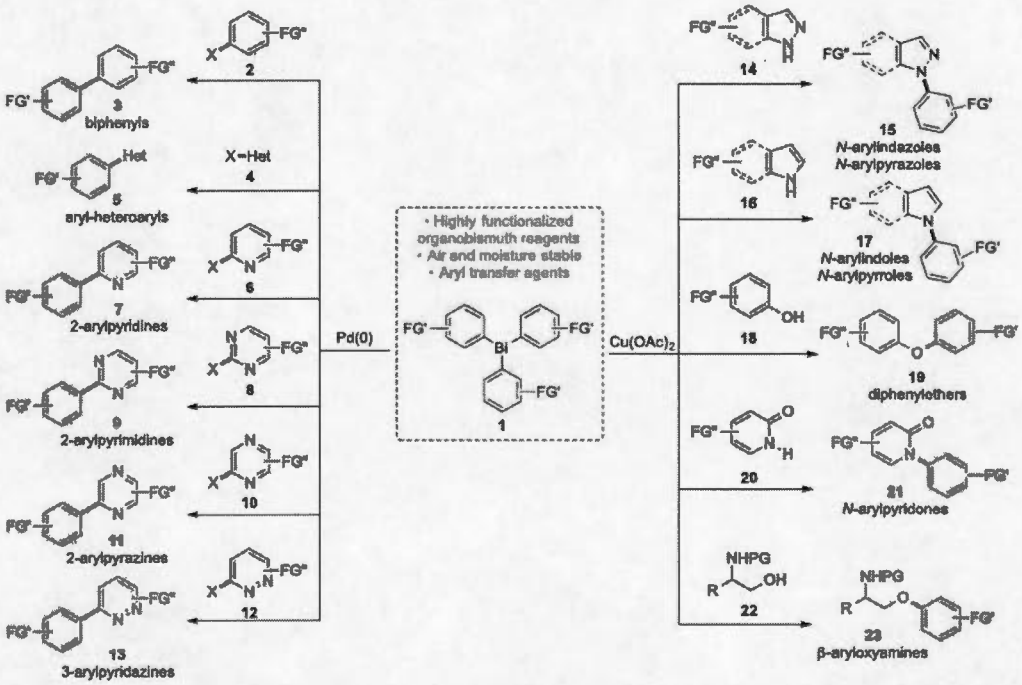
The preparation of complex organic molecules relies on our ability to form new bonds in a controlled fashion. In order to accomplish this task, access to efficient methods that allow the construction of new bonds in the presence of functional groups is essential. In addition, to be applicable to the context of medicinal chemistry, these methods should ideally be sufficiently simple and robust to be amenable to parallel chemistry, thus enabling the preparation of libraries of pharmaceutically relevant compounds.[1]

Organometallic reagents have revolutionized the field of organic chemistry by facilitating the formation of challenging bonds. However, in some cases, these reagents suffer from severe limitations such as air and moisture sensitivity, pyrophoricity, low stability, and poor functional group compatibility. Recently, the disclosure of methods by Knochel for the preparation of functionalized organometallic reagents has contributed to solving some of the issues that are intrinsically linked to organometallic species.

Organobismuthanes are a class of organometallic reagents that possess a carbon-bismuth bond. These reagents can be prepared from inexpensive and non toxic bismuth salts. Arylbismuthanes are particularly attractive since they are air and moisture stable and since they can be purified by simple flash chromatography or by crystallization. Due to the weak strenght of the carbon-bismuth bond, organobismuth reagents are remarkably tolerant to numerous functional groups. The reactivity of organobismuth compounds is determined by the oxidation state of the bismuth center, with trivalent Bi(III) reagents acting as nucleophiles and pentavalent Bi(V) species behaving as electrophiles.[2] In the 1980's, Barton and Finet exploited this dual mode of reactivity to develop a series of metal-catalyzed reactions based on organobismuthanes.[3] More recently, the work of Condon and Rao[4] on organobismuthanes contributed to expand the application of this class of reagents in organic synthesis.

Our group has reported over the past years a portfolio of methods for the formation of C–C,[5] C–N,[6] and C–O[7] bonds using functionalized trivalent organobismuth reagents **1**. These methods allow the transfer of functionalized aryl groups on various scaffolds such as

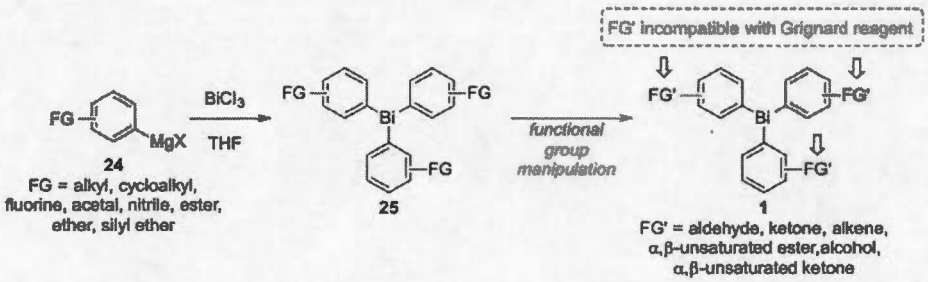
arenes **2**, heteroarenes **4**, pyridines **6**, pyrimidines **8**, pyrazines **10**, pyridazines **12**, indazoles and pyrazoles **14**, indoles and pyrroles **16**, phenols **18**, pyridones **20**, and 1,2-aminoalcohols **22**, giving access to a range of medicinally relevant compounds (**Scheme 1**). These methodologies are simple to operate, require almost no optimization of the reaction conditions, and tolerate a wide array of functional groups on both coupling partners.



Scheme 1. Triarylbismuthanes in arylation reactions: access to highly functionalized and medicinally relevant compounds

Triarylbismuth reagents **25** can be easily accessed via the addition of the corresponding Grignard reagents **24** onto bismuth chloride (**Scheme 2**). However, due to the reactive nature of organomagnesium reagents, functional groups possessing electrophilic centers or acidic functions cannot be introduced on the organobismuth species using this approach. Condon reported an elegant and powerful method to prepare functionalized organobismuth reagents by addition of organozinc reagents obtained from a

cobalt-zinc metal-halogen exchange reaction on aryl halides. While this method is quite general, we felt that alternative procedures were still desirable to provide more flexibility in the preparation of organobismuthanes **25**. The strategy that we explored consists in introducing the incompatible functional group *à postériori* by performing functional group transformations directly on species **25**. In the course of our studies, we found that the C–Bi bonds in organobismuthanes **25** are surprisingly resistant to a wide range of acidic, basic, reductive, and even oxidative conditions, thus enabling the transformation of the functional group FG in **25** into more elaborated functional groups FG' as shown in **1**. We would like to report herein the preparation of highly functionalized triarylbismuth reagents using this approach and their use in copper and palladium-catalyzed C–C, C–N, and C–O bond formation reactions.



Scheme 2. Synthesis of highly functionalized organobismuthanes by functional group manipulation

We began by synthesizing a set of organobismuthanes **25** bearing inert groups via the addition of organomagnesium reagents **24** to bismuth chloride (**Figure 1**). The Grignard reagents **24** were prepared from the corresponding aryl halides **26** through conventional methods involving metallic magnesium at reflux of ether or THF. Using this approach, eighteen different *ortho, meta,* and *para* substituted triaryl- and heteroarylbismuthanes were synthesized in moderate to excellent yield.

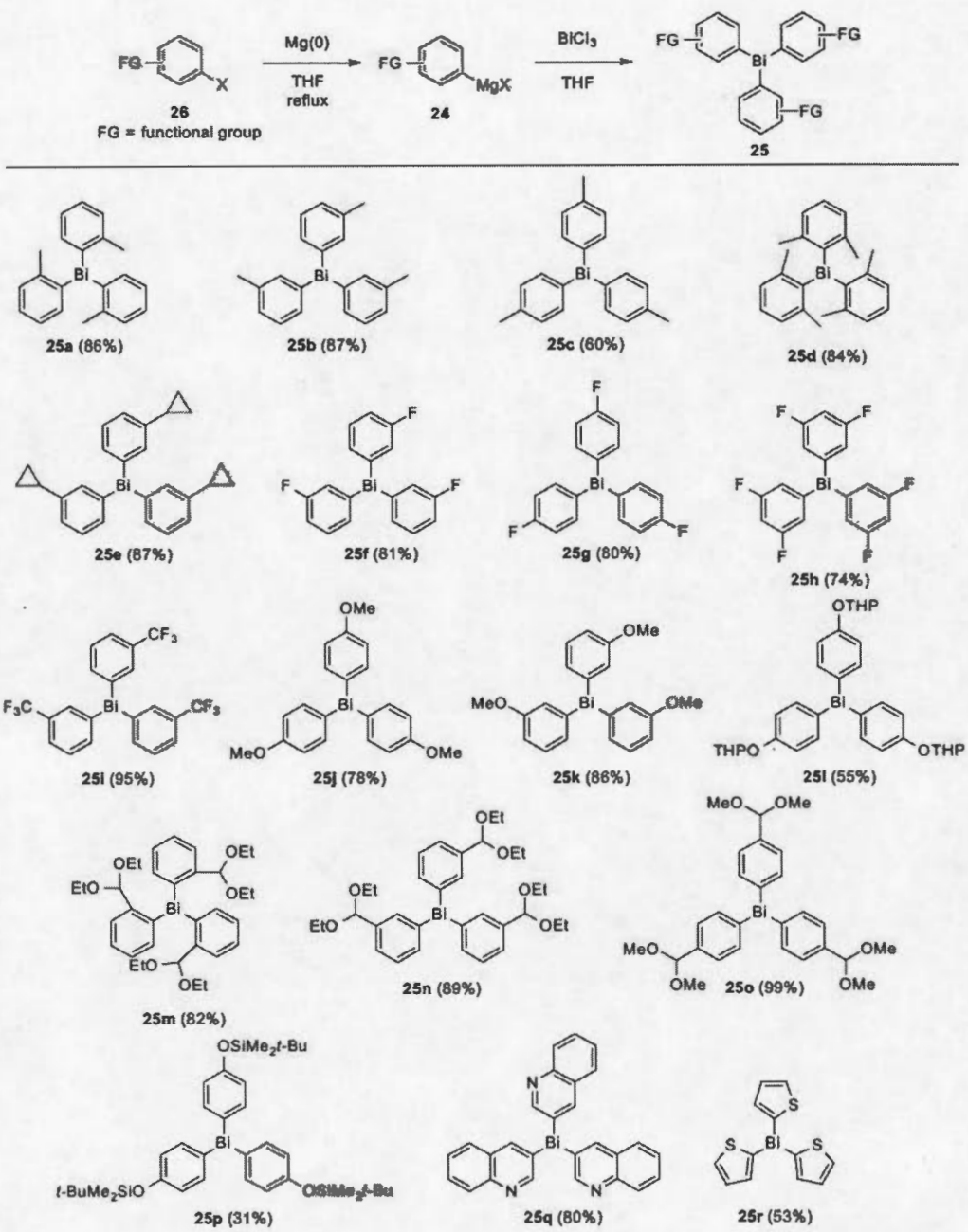
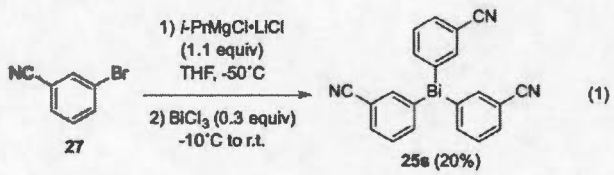
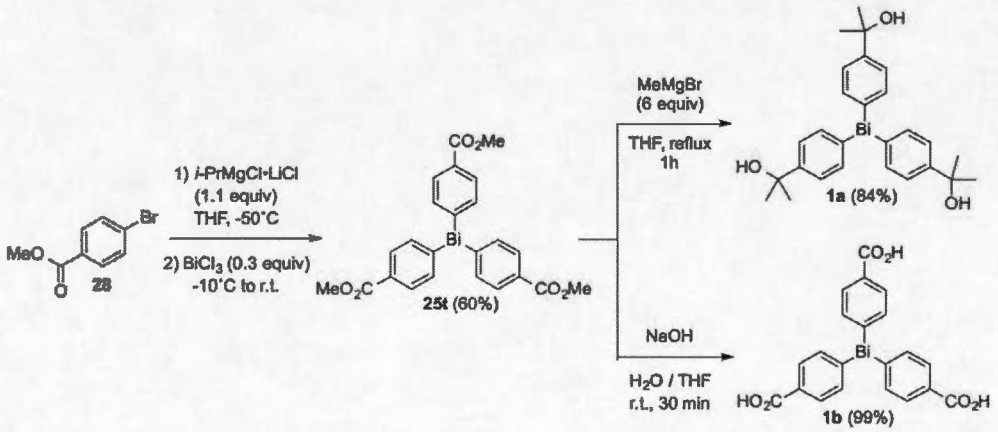


Figure 1. Preparation of functionalized organobismuthanes directly from organomagnesium reagents

For the introduction of more reactive groups such as nitriles, the standard procedure described in **Figure 1** was slightly modified since the Grignard reagent could not be prepared by refluxing *meta*-cyanophenylbromide **27** with metallic magnesium. Instead, the desired Grignard was generated from bromide **27** using Knochel's procedure. Addition of the organomagnesium reagent thus obtained over bismuth chloride followed by usual work-up afforded tris(3-cyanophenyl)bismuthane **25s**, albeit in low yield **(Eq. 1)**.

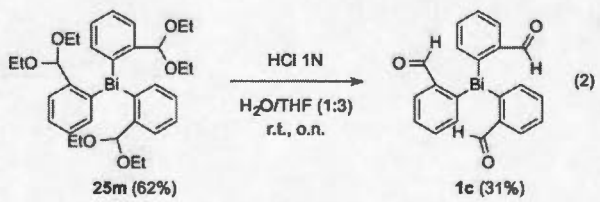


As a point of entry into the exploration of group manipulation on organobismuthanes, we synthesized triaryl bismuth reagent **25t** where an ester is present at the *para* position or the aromatic group, from the corresponding Grignard reagent, itself prepared from *para*-bromo methylbenzoate **28** using Knochel's procedure **(Scheme 3)**. Starting from **25t**, the ester was transformed into the corresponding tertiary alcohol **1a** by addition of methylmagnesium bromide and acid **1b** by saponification respectively. These two transformations demonstrate that the carbon–bismuth bonds in arylbismuthanes are resistant to organometallic and basic aqueous conditions.



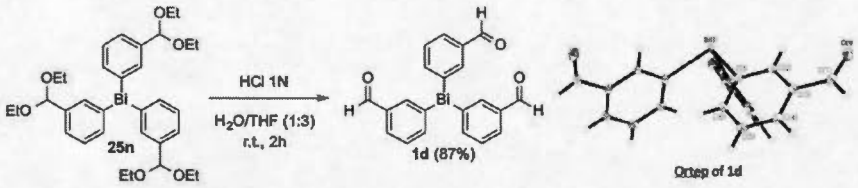
Scheme 3. Preparation of tris(4-(1-hydroxy-1-methyl)ethylphenyl)bismuthane **1a** and tris(4-carboxyphenyl)bismuthane **1b** by Grignard addition and saponification of triester **25t**

Due to their high electrophilicity, aldehydes cannot be present on organomagnesium reagents. The preparation of organometallic reagents bearing aldehydes must therefore involve less electropositive metals such as lead, tin, boron, zinc or indium. However, the toxic nature of tin and lead greatly limits the use of the corresponding organometallic species in synthesis. While many organoboronic acids bearing aldehyde groups are commercially available, their use in metal-catalyzed reaction often require extensive optimization of the conditions. Conversely, arylzinc reagents bearing aldehyde functions have proven to be very useful in palladium cross-coupling reactions, but their sensitivity to moisture and air make them not suitable for applications in parallel chemistry. Finally, while organoindium have generated great interest in the synthetic community over the past decade, the cost of indium represents a non negligible issue to their application in the synthesis of medicinal chemistry compounds. In that context, organobismuthanes bearing aldehydes can fill an important need in organic synthesis. Starting from tris(2-diethoxymethyl)phenylbismuthane **25m**, we performed the hydrolysis of the acetal function to generate the tris-formyl derivative **1c** in modest yield (**Eq. 2**).



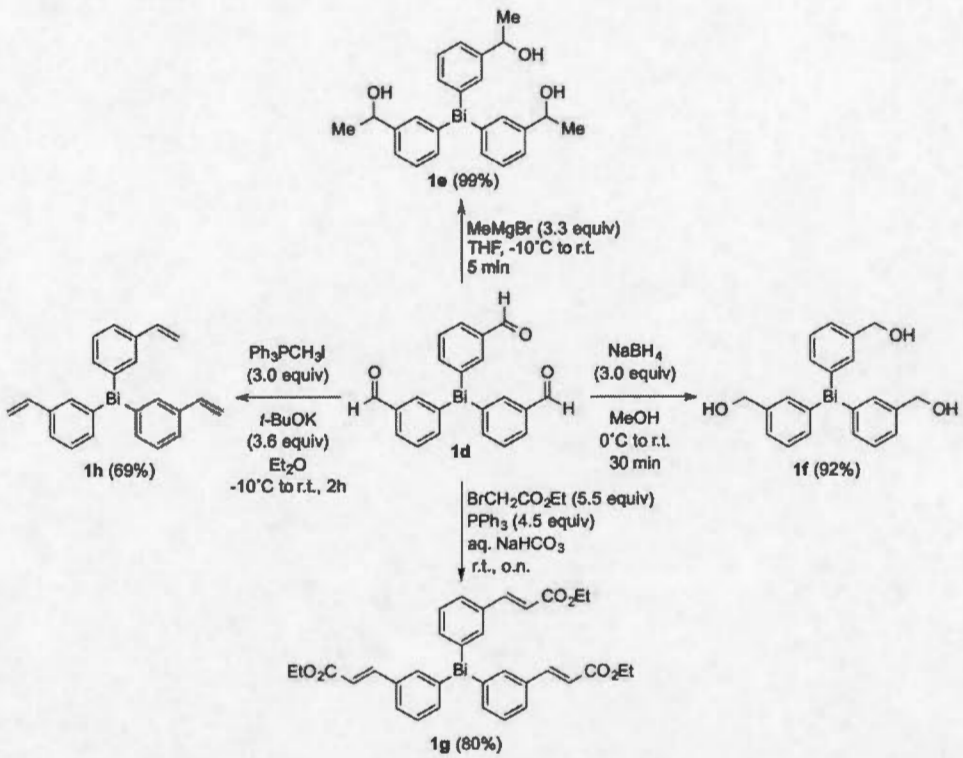
25m (62%) **1c (31%)** (2)

Using the same sequence, tris(3-formylphenyl)bismuthane **1d** was prepared from organobismuthane **25n** (**Scheme 4**). These two examples show that organobismuthanes are inert to aqueous acidic conditions, demonstrating the robustness of these reagents.



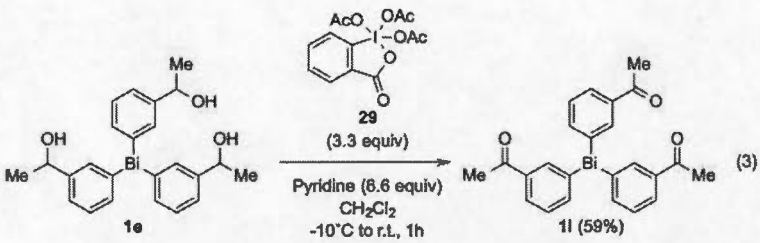
Scheme 4. Synthesis and X-ray structure of tris-(3-formylphenyl)bismuthane **1d**

We then utilized reagent **1d** as a point of diversification for the introduction of other functional groups (**Scheme 5**). For instance, the addition of methylmagnesium bromide on **1d** provided the corresponding tris(3-(1-hydroxyethyl)phenyl)bismuthane **1e** in excellent yield. The reduction of the aldehyde on **1d** was also accomplished using sodium borohydride, affording tris(3-(hydroxymethyl)phenyl)bismuthane **1f** in 93% yield. Next, olefination reactions using Horner-Emmons-Wadsworth[8] or Wittig[9] conditions were performed, leading to the corresponding cinnamyl and vinyl derivatives **1g** and **1h**. These examples show that organobismuthanes are resistant to organometallic and reductive agents as well as phosphorus ylides.

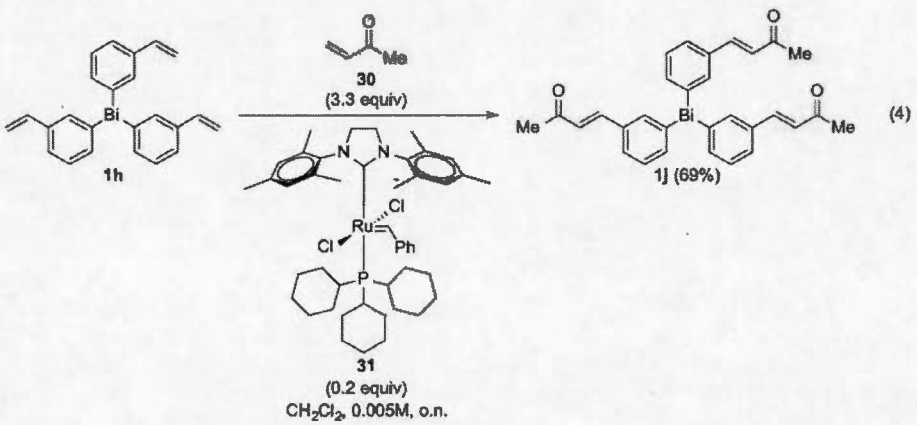


Scheme 5. Synthesis of highly functionalized organobismuthanes **1e-h** by derivatization of tris(3-formylphenyl)bismuthane **1d**

We next focused our efforts on the introduction of a ketone on the organobismuth reagent and envisaged achieving achieving this by oxidizing the secondary alcohol in **1e** (**Eq. 3**). However, since trivalent organobismuthanes can be oxidized into their pentavalent counterparts using oxidizing agents, it was not clear from the onset if the bismuth (III) center in **1e** would tolerate oxidizing conditions. Pleasently, the tris-methyl ketone **1i** was obtained in moderate yield using Dess-Martin periodinane **29** as the oxidizing agent.



We then elected to synthesize organobismuthane **1j** by conducting a cross-metathesis reaction between the tris-vinyl species **1h** and methyl vinyl ketone **30**. After testing a few metathesis catalysts, we found that **1j** could be obtained in good yield and with exclusive *E* configuration using Grubbs-II catalyst. **(Eq. 4)**.



Access to efficient methods that lead to the formation of sp^2-sp^2 bonds is particularly important in organic chemistry as 38% of the bioactive compounds prepared in the pharmaceutical industry contain a biaryl moiety. The discovery of palladium-catalyzed cross-coupling reactions has revolutionized the way chemists construct carbon-carbon bonds. In fact, according to a recent survey, 11.5% of the reactions conducted in the pharmaceutical industry during drug discovery phases consist of a palladium-catalyzed cross-coupling reaction. In another study, this number was even higher and was estimated to be around 22% of all reactions conducted by medicinal chemists. Therefore, it is no

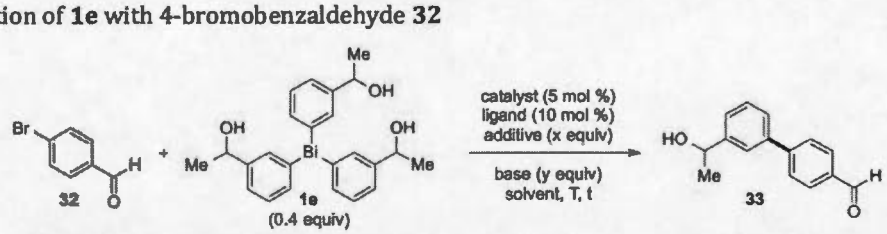
surprise that the Suzuki reaction, which consists in the coupling of an organoboronic acid with an aryl halide, is the 8th most utilized reaction in medicinal chemistry.

The popularity of palladium-catalyzed cross-coupling reactions is intimately linked to the availability of organometallic reagents that show little toxicity and that can be easily prepared, stored, and handled. Although this is the case for organoboronic acids, other reagents often suffer from several limitations. For example, organotin reagents are toxic and are usually avoided in the pharmaceutical industry while organozinc reagents are highly pyrophoric and moisture sensitive and must therefore be manipulated under anhydrous and oxygen-free conditions. In other cases such as organomagnesium reagents, low functional group compatibility is usually observed.

With our functionalized organobismuthanes in hand, we next explored their reactivity in cross-coupling reactions using conditions that we previously reported for the coupling involving 2-haloazines and diazines. One important aspect of arylbismuth reagents is their ability to deliver three aryl groups per equivalent of organometallic reagent in cross-coupling reactions. Therefore, we performed our optimization of reaction conditions using 0.4 equivalent of the organobismuthane. Among other important goals, we wanted to minimize the amount of catalyst, to use mild bases, and to use the lowest possible temperature and reaction time for this transformation. To investigate the functional group tolerance and to facilitate the substrate analysis by NMR-spectroscopy, we searched for conditions that would allow the cross-coupling between triarylbismuthane **1e** and 4-bromobenzaldehyde **32**. Using our previously reported conditions, we obtained the desired cross-coupling product **33** in only 37% yield (**Table 1**, entry 1). The observed low yield shows that the coupling of highly functionalized organobismuthanes represents a substantial challenge and commands the fine-tuning of all parameters in order to identify more efficient conditions for this transformation. Suspecting that the high temperature was potentially leading to decomposition of the reagent or the the product, we next performed the coupling reaction at 80°C but obtained a similar yield of **33** (entry 2). Changing the catalyst for $PdCl_2(PPh_3)_2$ (entry 3), $Pd(OAc)_2$/S-Phos (entry 4), $Pd(OAc)_2/PPh_3$ (entry 5) or PEPSI-*i*Pr (entry 6) did not provide any improvement in the yield of the reaction. Organ

recently reported the beneficial effect of lithium salts on cross-coupling reactions. Using this information, we found that a substantial amelioration in the yield of the reaction was obtained using 2.0 equivalents of lithium chloride as an additive (entry 7). Changing the solvent for THF (entry 8), toluene (entry 9) or a mixture of DMF and HMPA (entry 10) was detrimental for the reaction or at best inconsequential. The use of a stronger base such as potassium *tert*-butoxide led to a drastic drop in the yield of the reaction (entry 11). In addition, while potassium carbonate provided similar yields as cesium carbonate (entry 12), we found that potassium phosphate was much more efficient as a base in this transformation, providing the desired cross-coupling product **33** in 82% isolated yield (entry 13). Lowering the number of equivalents of lithium chloride (entry 14) or potassium phosphate (entry 15) led to an erosion in the yield of the reaction. Although water was somewhat tolerated, no improvement in the yield was observed using a 5:1 ratio of DMF:water (entry 16). The optimized conditions identified from this study represent a considerable improvement over our previously reported protocol since the coupling can now be performed at lower temperature and in lesser time.

Table 1. Optimization of reaction conditions for the palladium-catalyzed cross-coupling reaction of **1e** with 4-bromobenzaldehyde **32**



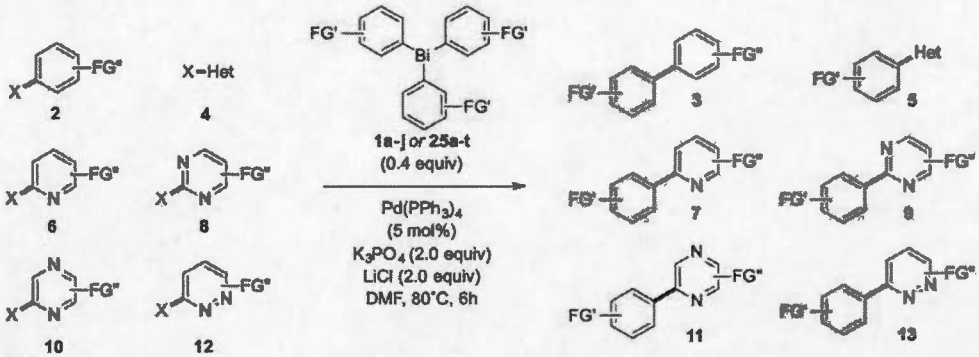
entry	catalyst	ligand	additive (x equiv)	base (y equiv)	solvent	T (°C)	t (h)	yield (%)[a]
1	$Pd(PPh_3)_4$	N.A.	N.A.	Cs_2CO_3 (2 equiv)	DMF	130	18	37
2	$Pd(PPh_3)_4$	N.A.	N.A.	Cs_2CO_3 (2 equiv)	DMF	80	6	36
3	$PdCl_2(PPh_3)_2$	N.A.	N.A.	Cs_2CO_3 (2 equiv)	DMF	80	6	31
4	$Pd(OAc)_2$	S-Phos	N.A.	Cs_2CO_3 (2 equiv)	DMF	80	6	7
5	$Pd(OAc)_2$	PPh_3	N.A.	Cs_2CO_3 (2 equiv)	DMF	80	6	31
6	PEPSI-iPr	N.A.	N.A.	Cs_2CO_3 (2 equiv)	DMF	80	6	23
7	$Pd(PPh_3)_4$	N.A.	LiCl (2 equiv)	Cs_2CO_3 (2 equiv)	DMF	80	6	64

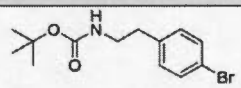
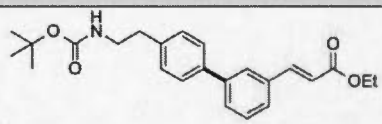
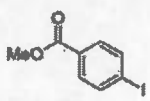
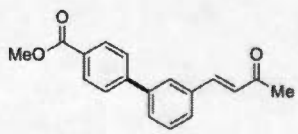
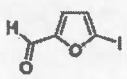
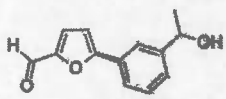
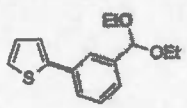
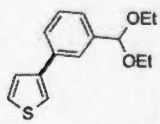
8	$Pd(PPh_3)_4$	N.A.	LiCl (2 equiv)	Cs_2CO_3 (2 equiv)	THF	80	6	13
9	$Pd(PPh_3)_4$	N.A.	LiCl (2 equiv)	Cs_2CO_3 (2 equiv)	Toluene	80	6	25
10	$Pd(PPh_3)_4$	N.A.	LiCl (2 equiv)	Cs_2CO_3 (2 equiv)	DMF/HMPA	80	6	59
11	$Pd(PPh_3)_4$	N.A.	LiCl (2 equiv)	*t*-BuOK (2 equiv)	DMF	80	6	14
12	$Pd(PPh_3)_4$	N.A.	LiCl (2 equiv)	K_2CO_3 (2 equiv)	DMF	80	6	69
13	**$Pd(PPh_3)_4$**	**N.A.**	**LiCl (2 equiv)**	**K_3PO_4 (2 equiv)**	**DMF**	**80**	**6**	**82**
14	$Pd(PPh_3)_4$	N.A.	LiCl (1 equiv)	K_3PO_4 (2 equiv)	DMF	80	6	57
15	$Pd(PPh_3)_4$	N.A.	LiCl (2 equiv)	K_3PO_4 (1 equiv)	DMF	80	6	48
16	$Pd(PPh_3)_4$	N.A.	LiCl (2 equiv)	K_3PO_4 (2 equiv)	DMF/H_2O[b]	80	6	73

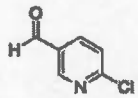
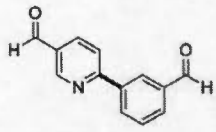
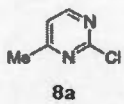
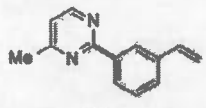
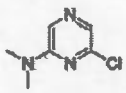
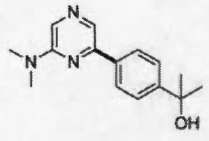
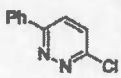
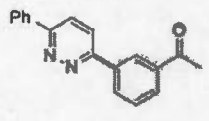
[a] Isolated yield of pure product. [b] DMF/H_2O (5:1 ratio)

Having optimized the conditions for the cross-coupling reaction involving functionalized organobismuthanes, we next investigated the scope of the method using selected aryl halides **2**, heteroarylhalides **4**, 2-halopyridines **6**, 2-halopyrimidines **8**, 2-halopyrazines **10**, and 2-halopyridazines **12** (Table 2). The choice of the electrophiles was motivated by the presence of functional groups that would demonstrate the applicability of our protocol in the preparation of highly functionalized compounds. Therefore, 4-(*N*-BOC-aminoethyl)bromobenzene **2a**, 4-iodo methyl benzoate **2b**, 2-iodo-4-furaldehyde **4a**, 2- and 3-bromothiophene **4b** and **4c**, 6-chloropyridine-3-carboxaldehyde **6a**, 2-chloro-4-methylpyrimidine **8a**, 2-chloro-6-dimethylaminopyrazine **8a**, and 3-chloro-6-phenylpyridazine **12a** were engaged in cross-coupling reactions with organobismuthanes **1a-j** and **25a-t** to afford the corresponding products in low to excellent yield. These example demonstrate that our method tolerate a wide diversity of functional groups on the electrophile (BOC-protected amines (**3a**), esters (**3b**), aldehydes (**5a**), and dialkyamines (**13a**)) as well as on the organobismuthane (cinnamyl ester (**3a**), acetal (**5b,c**) and aldehyde (**7a**)). Perhaps more fascinating is the ability of this method to deliver in workable yields aryl groups that possess functions that are susceptible to arylation, elimination, or oxidation such as an α,β-unsaturated ketone (**3b**), a secondary alcohol (**5a**), a vinyl group (**9a**) and a methylketone (**13a**).

Table 2. Palladium-catalyzed cross-coupling reaction of highly functionalized organobismuthanes **1a-j** and **25a-t** with arylhalides (**2**), heteroarylhalides (**4**), halopyridines (**6**), halopyrimidines (**8**), halopyrazines (**10**), and halopyridazines (**12**)



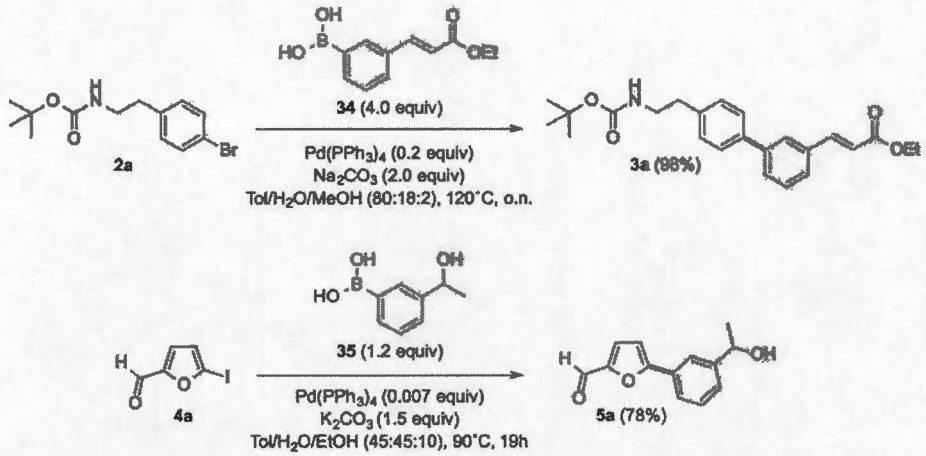
entry	electrophile	Ar_3Bi	product	yield (%)[a]
1	 2a	1g	 3a	91
2	 2b	1j	 3b	43
3	 4a	1e	 5a	84
4	 4b	25n	 5b	37
5	 4c	25n	 5c	28

6	 **6a**	**1d**	 **7a**	36
7	 **8a**	**1h**	 **9a**	21
8	 **10a**	**1a**	 **11a**	42
9	 **12a**	**1i**	 **13a**	25

[a] Isolated yield of pure product.

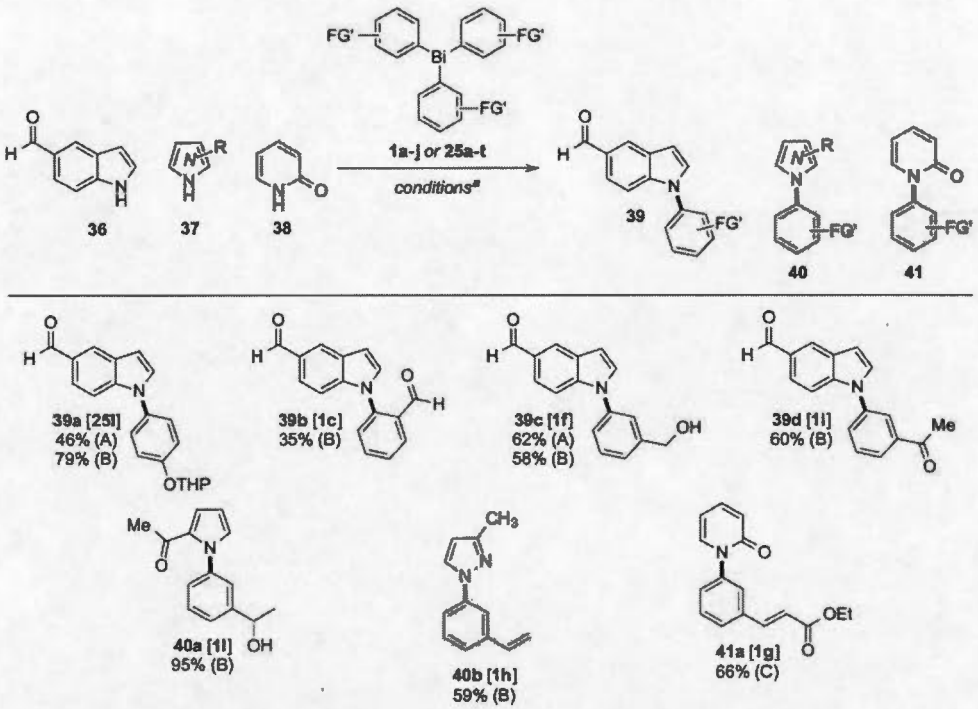
In order to calibrate our method with respect to other classical cross-coupling reactions, we performed the coupling between 4-(*N*-BOC-aminoethyl)bromobenzene **2a** and boronic acid **34** using conditions from the literature[10] and obtained the corresponding product **3a** in 98% yield (**Scheme 6**). Interestingly, the reported procedure required 4.0 equivalents of boronic acid at 120°C overnight to achieve a good yield. By comparison, the same product was obtained using the 0.4 equivalent of the corresponding organobismuthane **1g** at 80°C in 6 hours (**Table 2**, entry 1).

We then prepared compound **5a** from boronic acid **35** using conditions from the literature (**Scheme 6**).[11] Again, long reaction times were needed to obtain a good yield of **5a** from the boronic acid while our protocol involving organobismuthane **1e** afforded the same compound in slightly higher yield in only 6 hours (**Table 1**, entry 3).



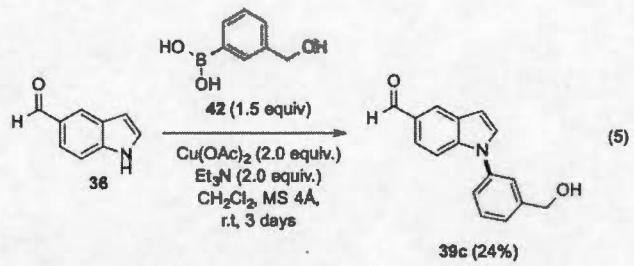
Scheme 6. Preparation of derivatives **3a** and **5a** by Suzuki cross-coupling reactions between aryl and heteroaryl halides **2a** and **4a** and boronic acids **34** and **35**

We recently reported a copper-catalyzed protocol for the *N*-arylation of azoles, diazoles and pyridones using organobismuthanes and demonstrated that a wide array of functional groups are tolerated in this transformation. To further expand on the functional group diversity of this method, we tested some of the highly functionalized organobismuthanes prepared in this work in the *N*-arylation reaction. As illustrated in **Scheme 7**, moderate to excellent yields of the desired *N*-arylated products were obtained using the previously reported conditions. These examples demonstrate that the method is extremely general and can be used to transfer aryl groups possessing a benzylic alcohol (**39c**), a methyl ketone (**39d**), a secondary alcohol (**40a**), a vinyl group (**40b**) and an α,β-unsaturated ester (**41a**).

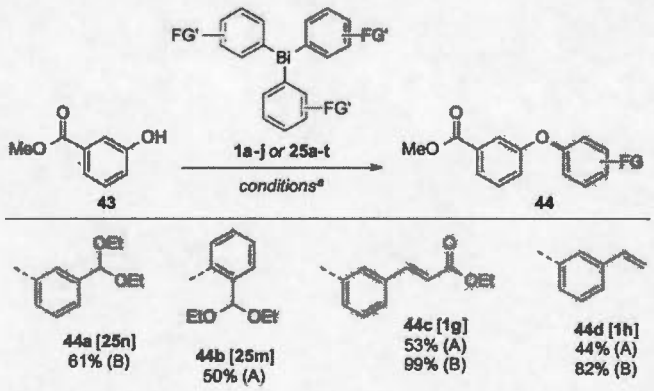


Scheme 7. *N*-Arylation of indoles **36**, pyrroles and pyrazoles **37**, and pyridones **38** using highly functionalized organobismuthanes **1a-j** and **25a-t**. The numbers in brackets indicate the organobismuthane used for the synthesis of each compound. [a] Conditions: Method A: Ar_3Bi (1.0 equiv), $Cu(OAc)_2$ (0.1 equiv), pyridine (1.0 equiv), CH_2Cl_2, O_2, 50°C; Method B: Ar_3Bi (1.0 equv), $Cu(OAc)_2$ (1.0 equiv), pyridine (3.0 equiv), CH_2Cl_2, O_2, 50°C; Method C: Ar_3Bi (1.0 equv), $Cu(OAc)_2$ (1.0 equiv), pyridine (3.0 equiv), CH_2Cl_2, air, 50°C.

To evaluate the efficiency of our protocol, we next prepared compound **39c** from organoboronic acid **42** using a method from the literature that involves 2.0 equivalents of copper acetate, 2.0 equivalent of triethylamine in dichloromethane in the presence of molecular sieves (**Eq. 5**).[12] After 3 days at room temperature, only 24% of the desired product was obtained. By comparison, the same compound was prepared in 62% overnight using the corresponding organobismuthane **1f** (**Scheme 7**).

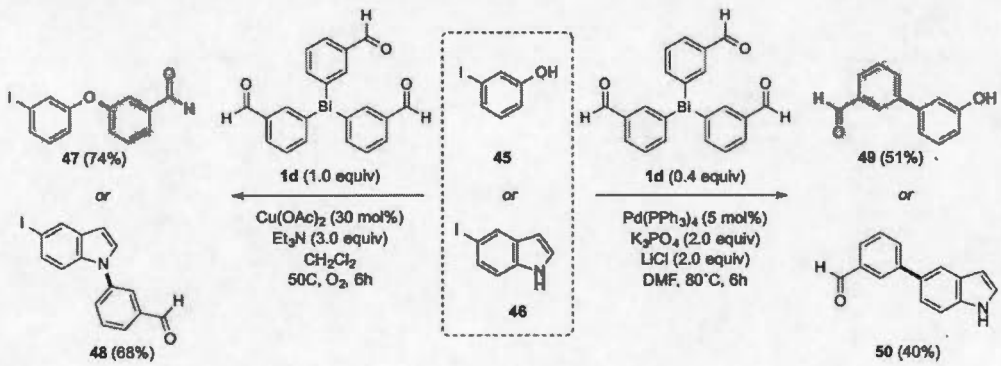


We next evaluated the applicability of some of the prepared organobismuthanes herein in the *O*-arylation reaction of 3-hydroxymethylbenzoate using a protocol that we reported in 2013. As shown in **Scheme 8**, our method proved very general and allowed the transfer of aryl groups possessing a variety of groups such as an acetal in *meta* or even *ortho* position (**44a,d**), an α,β-unsaturated ester (**44b**) and a vinyl group (**44c**). We demonstrated previously that this method is comparable or to existing *O*-arylation methods where 2.5 equivalents of organoboronic acids are utilized to achieve good yield of the desired diarylether.



Scheme 8. *O*-Arylation of 3-hydroxy methyl benzoate **43** using highly functionalized organobismuthanes **1a-j** and **25a-t**. The numbers in brackets indicate the organobismuthane used for the synthesis of each compound. [a] Conditions: Method A: Ar_3Bi (1.0 equiv), $Cu(OAc)_2$ (1.0 equiv), Et_3N (3 equiv), CH_2Cl_2, 50°C, air, 3h; Method B: Ar_3Bi (1.0 equiv), $Cu(OAc)_2$ (0.3 equiv), Et_3N (3 equiv), CH_2Cl_2, 50°C, O_2, 16h.

Finally, we explored the orthogonal transfer of aryl groups on substrates bearing at the same time an aryl halide function and either a phenol or an indole (**Scheme 9**). While this might appear as a trivial experiment, one must realize that the presence of an acidic group such as a phenol or an indole could lead to dehalogenation of the electrophile during the palladium cross-coupling reaction. Gratifyingly, the protocol developed in **Table 1** proved to be very efficient in the context of palladium cross-coupling reaction with 3-iodophenol **45** and 5-iodoindole **46**, affording products **49** and **50** respectively in moderate yields. In addition, the aryl transfer could be directed regioselectively on the oxygen of **45** or the nitrogen of **46** using copper acetate to afford **47** and **48**, in good yield.



Scheme 9. Orthogonal *N*- and *O*-arylation vs *C*-arylation of 3-iodophenol **45** and 5-iodoindole **46** using tris(3-formylphenyl)bismuthane **1d**

CONCLUSION

In summary, we demonstrated that highly functionalized triarylbismuthanes can be prepared by functional group manipulation using acidic, basic, nucleophilic, or reducing conditions or using organometallic reagents. This approach gives access to unique organobismuthanes for which corresponding organoboronic acids are not avalaible. We then developed an improved protocol for the palladium-catalyzed cross-coupling reaction involving these highly functionalized reagents. The modified procedure, which was utilized to prepare highly substituted biaryl substrates, involves lithium chloride as an additive and potassium phosphate as a base and requires shorter reaction times and temperatures. The

organobismuthanes prepared using the functional group manipulation approach were then used in the *N*-arylation of azoles and diazoles and in the *O*-arylation of phenols and pyridones, affording highly functionalized products. The protocols reported herein were shown to be equivalent or superior to other exisiting methods using organoboronic acids. The *C*-, *N*-, and *O*-arylation procedures developed in this work constitute an efficient and general portfolio of methods for the preparation of medicinally relevant scaffolds.

EXPERIMENTAL SECTION

Genereal Information. Unless otherwise indicated, all reactions were run under argon in non-flame dried glassware. For reactions performed under oxygen, 99.6% extra dry oxygen was used. Unless otherwise stated, commercial reagents were used without further purification. Grignard reagents were prepared by conventional methods using metallic magnesium or via Knochel's procedure.[1] Triphenylbismuth and anhydrous bismuth chloride 99.999% were purchased from Strem Chemicals. Triarylbismuthanes were prepared according to procedures that we previously reported.[2,3] Anhydrous solvents were obtained using a MBRAUN (model MB-SPS 800) encapsulated solvent purification system. The evolution of reactions was monitored by analytical thin-layer chromatography using silica gel 60 F254 precoated plates. Flash chromatography was performed employing 230-400 mesh silica (Silicycle) using the indicated solvent system according to standard techniques.[4] Melting points were taken on an Electrothermal Mel-TEMP and are uncorrected. Nuclear magnetic resonance spectra (^{1}H, ^{13}C) were recorded on a Bruker Avance-III 300MHz spectrometer. Chemical shifts for ^{1}H-NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qt = quintuplet, dd = doublet of doublet, m = multiplet), coupling constant *J* in Hz and integration. Chemical shifts for ^{13}C spectra are recorded in parts per million from tetramethylsilane using the central peak of deuterochloroform (δ 77.16 ppm) as the internal standard. IR spectra were recorded on a Thermo Scientific Nicolet 6700 PT-IR from thin films and are reported in reciprocal centimeters (cm^{-1}). HRMS were performed at Université du Québec à Montréal (nanoQAM

center) on Agilent Technologies, LC 1200 Series / 6210 TOF LCMS analyzer using the electrospray (ESI) mode.

Synthesis of triarylbismuthanes. General procedure. In a flask equipped with a magnetic stir bar and a condenser, bismuth chloride (500 mg, 1.6 mmol) was dissolved in anhydrous THF (23 mL) under argon and was cooled to –10°C (ice/acetone bath). The organomagnesium reagent (5.23 mmol) was slowly added dropwise under argon. The reaction mixture was stirred at room temperature for one hour and heated at 65°C for 30 minutes. After cooling to r.t., the solution was diluted with sat. aq. $NaHCO_3$ (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (2 x 100 mL), sat. aq. NaCl (2 x 100 mL), dried over $Na_2S_2O_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using the indicated solvent system to afford the desired triarylbismuthane.

Tris(4-((*tert*-butyldimethylsilyl)oxy)phenyl)bismuthine (25p). The general procedure was followed on a 1.6 mmol scale starting from bismuth chloride and (4-((*tert*-butyldimethylsilyl)oxy)phenyl)magnesium bromide. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford tris(4-((*tert*-butyldimethylsilyl)oxy)phenyl)bismuthine **25p** as a white solid (418 mg, 31%): R_f 0.89 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 8.3 Hz, 2H), 6.83 (d, J = 8.3 Hz, 2H), 0.97 (s, 9H), 0.18 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 155.4, 145.9, 138.8, 129.4, 122.4, 120.2, 25.7, 18.2, -4.3; IR (neat) 2956, 2929, 2886, 2857, 1578, 1487, 1254, 1171, 913; HRMS (ESI) calcd for $C_{36}H_{57}BiO_3Si_3$: 830.3419, found 869.3075 $(M+K)^+$.

4, 4', 4''-Bismuthinetriyltribenzoic acid (1b). A solution of aqueous NaOH (3 mL, 1M) was added slowly to a solution of trimethyl 4,4',4''-bismuthinetriyltribenzoate **25t** (50 mg, 0.08 mmol) in anhydrous THF (3 mL). After 30 min, the reaction mixture was quenched with HCl (3 mL, 1M) and diluted with EtOAc (10 mL). The organic layer was washed with sat. aq. NaCl (3 x 10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford 4, 4', 4''-bismuthinetriyltribenzoic acid **1b** as a white solid (50 mg, quant.): R_f 0.45 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, MeOD) δ 8.02 (d, J = 8.1 Hz, 2H), 7.87 (d, J = 8.1 Hz, 2H); IR (neat) 3471, 3086, 2963, 2924, 2680, 2565, 1686, 1584, 1453, 1421, 1324, 1290, 924, 707; HRMS (ESI) calcd for $C_{21}H_{15}BiO_6$: 572.0672, found 571.0615 $(M-H)^-$.

2, 2', 2''-Bismuthinetriyltribenzaldehyde (1c). Bismuth chloride (1.7 g, 5.33 mmol) was dissolved in anhydrous THF (60 mL) and was cooled to –10°C (ice-acetone bath) and 2-(benzaldehydediethylacetal)magnesium bromide (44 mL, 17.6 mmol) was slowly added dropwise under argon. The reaction mixture was stirred at room temperature (r.t.) for one hour and heated at 65°C for 30 minutes. After cooling to r.t., the solution was diluted with sat. aq. $NaHCO_3$ (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (2 x 50 mL), sat. aq. NaCl (2 x 50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified on silica gel (5% EtOAc/hexanes) to afford tris(2-(diethoxymethyl)phenyl)bismuthine **25m** as a white solid (3.3 g, 82%): R_f 0.81 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 6.5 Hz, 1H), 7.60 (d, J = 7.3 Hz, 1H), 7.30 (td, J = 7.2, 0.7 Hz, 1H), 7.13 (td, J = 7.3, 1.0 Hz, 1H), 5.53 (s, 1H), 3.55-3.34 (m, 4H), 1.01 (t, J = 7.0 Hz, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 162.5, 144.4, 140.5, 130.9, 127.4, 126.7, 104.2, 61.3, 14.9; IR (neat) 3049, 2973, 2928, 2871, 1438, 1336, 1204, 1108, 1050, 757; HRMS (ESI) calcd for $C_{33}H_{45}BiO_6$: 746.3020, found 769.2868 $(M+Na)^+$.

H_2O (10 mL) and HCl 18N (0.75 mL) were added at room temperature to a stirred solution of **25m** (1 g, 1.3 mmol) in THF (30 mL). The reaction mixture was stirred for overnight and then diluted with EtOAc (20 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (20 mL) and sat. aq. NaCl (3 x 20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford tris(2-formylphenyl)bismuthine **1c** as a yellow solid (213 mg, 31%): R_f 0.46 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.23 (s, 1H), 8.01 (dd, J = 7.5, 1.4 Hz, 1H), 7.60-7.54 (m, 2H), 7.33 (td, J = 7.3, 1.4 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 195.9, 142.2, 140.7, 136.8, 136.3, 127.6, 125.5; IR (neat) 3042, 2977, 2806, 2724, 1690, 1671, 1571, 1556, 1197, 835, 759; HRMS (ESI) calcd for $C_{21}H_{15}BiO_3$: 524.0825, found 525.0896 $(M+H)^+$.

Trimethanol(bismuthinetriyltris(benzene-3,1-diyl)) (1f). A solution of 3, 3', 3''-bismuthinetriyltribenzaldehyde **1d** (400 mg, 0.8 mmol) in MeOH (10 mL), was cooled to –10°C (acetone/ice bath) and $NaBH_4$ (90 mg, 2.4 mmol) was added. After 30 minutes, the reaction mixture was diluted with EtOAc (15 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (15 mL) and sat. aq. NaCl (3 x 15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified on silica gel (40%

EtOAc/hexanes) to afford trimethanol(bismuthinetriyltris(benzene-3,1-diyl)) **1f** as a white solid (392 mg, 92%): R_f0.50 (10% MeOH/EtOAc); ^{1}H-NMR (300 MHz, MeOD) δ 7.77 (s, 1H), 7.62 (d, *J* = 6.9 Hz, 1H), 7.37-7.28 (m, 2H), 4.53 (s, 2H); ^{13}C-NMR (75 MHz, MeOD) δ 156.7, 144.3, 137.6, 137.2, 131.4, 127.6, 65.3; IR (neat) 3314, 3038, 2923, 2869, 1563, 1412, 1203, 1012, 776; HRMS (ESI) calcd for $C_{21}H_{21}BiO_3$: 530.1295, found 553.1177 $(M+Na)^+$.

Tris(3-vinylphenyl)bismuthine (1h). To a solution of Ph_3PCH_3I (1 g, 2.46 mmol) in THF (4.5 mL) to -10°C, *t*-BuOK was added (2.95 mL, 2.95 mmol) and the solution was stirred during 30 min. To the yellow solution, the 3,3',3''-bismuthinetriyltribenzaldehyde **1d** (430 mg, 0.82 mmol) was added and the reaction was heated to r.t. After 2h, the reaction mixture was concentrated under reduced pressure. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford tris(3-vinylphenyl)bismuthine **1h** as a yellow oil (291 mg, 69%): R_f0.70 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) 7.78 (s, 1H), 7.58 (d, *J* = 5.9 Hz, 1H), 7.33-7.29 (m, 2H), 6.60 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.60 (d, *J* = 17.6 Hz, 1H), 5.14 (d, *J* = 10.9 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 155.4, 139.4, 137.2, 137.0, 135.5, 130.7, 125.8, 114.1; IR (neat) 3156, 3084, 3040, 3006, 2984, 2927, 1939, 1821, 1629, 1554, 1467, 1380, 991, 906, 791, 710.

1, 1', 1''-(Bismuthinetriyltris(benzene-3,1-diyl))triethanone (1i). A solution of 1, 1', 1''-(bismuthinetriyltris(benzene-3,1-diyl))triethanol **1e** (50 mg, 0.09 mmol) in CH_2Cl_2 (3 mL) was cooled to –10°C (acetone/ice bath) and pyridine (46 μL, 0.59 mmol) was added. After 5 minutes, Dess-Martin Periodinane (123 mg, 0.28 mmol) was added. After 1h, the reaction mixture was diluted with EtOAc (15 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (15 mL) and sat. aq. NaCl (3 x 15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford 1, 1', 1''-(bismuthinetriyltris(benzene-3,1-diyl))triethanone **1i** as a colorless oil (30 mg, 59%): R_f0.17 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.91 (t, *J* = 7.1 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 1H), 2.52 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 198.4, 142.2, 138.8, 137.1, 131.1, 131.0, 128.3, 26.8; IR (neat) 3051, 3008, 2923, 1678, 1578, 1559, 1356, 1255; HRMS (ESI) calcd for $C_{24}H_{21}BiO_3$: 566.1295, found 567.1400 $(M+H)^+$.

(*3E,3'E,3''E*)-4, 4', 4''-(Bismuthinetriyltris(benzene-3,1-diyl))tris(but-3-en-2-one) (1j). To a solution of tris(3-vinylphenyl)bismuthine **1h** (50 mg, 0.097 mmol) in CH_2Cl_2

(20 mL), Grubbs II catalyst **31** (16 mg, 0.019 mmol) and but-3-en-2-one **30** (43 mg, 0.32 mmol) were added. The solution was heated to 40°C and after 2h, the reaction mixture was concentrated under reduced pressure. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford (*3E,3'E,3''E*)-4, 4', 4''-(bismuthinetriyltris(benzene-3,1-diyl))tris(but-3-en-2-one) **1j** as a colorless oil (43 mg, 69%): R_f 0.63 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.75 (d, *J* = 7.1 Hz, 1H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.48-7.42 (m, 2H), 6.62 (d, *J* = 16.3 Hz, 1H), 2.34 (s, 3H).

4. General procedures for the arylation reactions. Compounds **3, 5, 7, 9, 11** and **13** were prepared according to the following procedure: In a sealed tube, the starting bromide, chloride or iodide (1.0 equiv.) was dissolved in *N,N*-dimethylformamide (4.0 mL). Potassium phosphate (2.0 equiv.) was added, followed by tetrakis(triphenylphosphine)palladium (0.05 equiv.), lithium chloride (2.0 equiv.) and triarylbismuth reagent (0.4 equiv.). Argon was bubbled in the reaction mixture for 1 minute. The tube was sealed and heated at 80°C for 6h. The reaction mixture was cooled to r.t., diluted with sat. aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (2 x 20 mL), sat. aq. NaCl (2 x 20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using hexanes/ethyl acetate as the eluent to afford the corresponding product.

3'-(1-Hydroxyethyl)-[1,1'-biphenyl]-4-carbaldehyde (33). The general procedure was followed on a 0.27 mmol scale starting from 4-bromobenzaldehyde **32.** The crude material was purified on silica gel (25% EtOAc/hexanes) to afford **33** as a yellow oil (44 mg, 72%): R_f 0.22 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.03 (s, 1H), 7.93 (d, *J* = 8.3 Hz, 2H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.65 (s, 1H), 7.53 (dt, *J* = 7.0, 1.8 Hz, 1H), 7.48-7.40 (m, 2H), 4.98 (q, *J* = 12.9 Hz, 1H), 2.18 (s(br), 1H), 1.54 (d, *J* = 6.5 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 192.1, 147.2, 146.8, 139.9, 135.3, 130.3, 129.2, 127.8, 126.5, 125.6, 124.5, 70.3, 25.4; IR (neat) 3422, 3059, 3032, 2971, 2923, 2836, 2731, 1689, 1603, 1170, 1077, 794; HRMS (ESI) calcd for $C_{15}H_{14}O_2$: 226.0994, found 227.1068 $(M+H)^+$.

***(E)*-Ethyl 3-(4'-(2-((*tert*-butoxycarbonyl)amino)ethyl)-[1,1'-biphenyl]-3-yl)acrylate (3a).** The general procedure was followed on a 0.17 mmol scale starting from *tert*-butyl 4-bromophenethylcarbamate **2a.** The crude material was purified on silica gel

(15% EtOAc/hexanes) to afford **3a** as a colorless oil (60 mg, 89%): R_f 0.52 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.77-7.72 (m, 2H), 7.60-7.47 (m, 3H), 7.42-7.39 (m, 2H), 7.05 (d, *J* = 8.3 Hz, 2H), 6.51 (d, *J* = 16.0 Hz, 1H), 4.57 (s(br), 1H), 4.27 (q, *J* = 14.3 Hz, 2H), 3.33 (q, *J* = 12.9 Hz, 2H), 2.74 (t, *J* = 7.0 Hz, 2H), 1.42 (s, 9H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.9, 155.9, 144.3, 141.2, 138.0, 135.2, 131.7, 130.6, 129.5, 128.9, 127.3, 126.8, 120.3, 118.9, 79.4, 60.6, 41.6, 35.7, 28.4, 14.4; IR (neat) 3437, 3363, 2977, 2931, 1703, 1637, 1508, 1488, 1365, 1163, 1036, 789.

***(E)*-Ethyl 3'-(3-oxobut-1-en-1-yl)-[1,1'-biphenyl]-4-carboxylate (3b).** The general procedure was followed on a 0.19 mmol scale starting from ethyl 4-iodobenzoate **2b**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **3b** as a yellow solid (23 mg, 43%): R_f 0.35 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.5 Hz, 2H), 7.77 (s, 1H), 7.67-7.62 (m, 3H), 7.60-7.55 (m, 2H), 7.52-7.47 (m, 1H), 6.78 (d, *J* = 16.3 Hz, 1H), 3.94 (s, 3H), 2.40 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 198.3, 166.9, 144.8, 142.9, 140.9, 135.2, 130.3, 129.6, 129.4, 129.3, 127.8, 127.7, 127.2, 127.1, 52.2, 27.7; IR (neat) 3031, 2993, 2943, 2850, 1720, 1669, 1435, 1282, 1191, 1112, 767; HRMS (ESI) calcd for $C_{18}H_{16}O_3$: 280.1099, found 281.1173 $(M+H)^+$.

5-(3-(1-Hydroxyethyl)phenyl)furan-2-carbaldehyde (5a). The general procedure was followed on a 0.23 mmol scale starting from 5-iodofuran-2-carbaldehyde **4a**. The crude material was purified on silica gel (30% EtOAc/hexanes) to afford **5a** as a yellow oil (41 mg, 83%): R_f 0.16 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.61 (s, 1H), 7.82 (s, 1H), 7.71-7.68 (m, 1H), 7.43-7.39 (m, 2H), 7.30 (d, *J* = 3.7 Hz, 1H), 6.83 (d, *J* = 3.7 Hz, 1H), 4.94 (q, *J* = 12.9 Hz, 1H), 2.34 (s(br), 1H), 1.51 (d, *J* = 6.5 Hz, 3H); ^{13}C-NMR (75MHz, $CDCl_3$) δ 177.4, 159.5, 151.9, 146.9, 129.2, 129.1, 126.9, 124.4, 123.8, 122.3, 107.9, 70.0, 25.4; IR (neat) 3416, 3103, 2972, 2916, 2871, 2821, 1663, 1516, 1265, 1071, 1028, 792; HRMS (ESI) calcd for $C_{13}H_{12}O_3$: 216.0786, found 217.0867 $(M+H)^+$.

2-(3-(Diethoxymethyl)phenyl)thiophene (5b). The general procedure was followed on a 0.30 mmol scale starting from 2-bromothiophene **4b**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **5b** as a colorless oil (29 mg, 37%): R_f 0.66 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.57 (dt, *J* = 6.8, 1.9 Hz, 1H), 7.42-7.37 (m, 2H), 7.34 (dd, *J* = 3.4, 0.9 Hz, 1H), 7.29-7.26 (m, 1H), 7.08 (q, *J* = 5.1 Hz, 1H), 5.54 (s, 1H), 3.71-3.52 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ

192.1, 142.7, 136.9, 135.4, 131.6, 129.6, 129.0, 128.7, 128.3, 127.2, 126.6, 125.8, 124.1; IR (neat) 3114, 3068, 2924, 2825, 2719, 1599, 1582, 1269, 1162, 791, 700.

3-(3-(Diethoxymethyl)phenyl)thiophene (5c). The general procedure was followed on a 0.30 mmol scale starting from 3-bromothiophene **4c**. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford **5c** as a colorless oil (22 mg, 28%): R_f 0.79 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.58-7.54 (m, 1H), 7.49-7.48 (m, 1H), 7.43-7.34 (m, 4H), 5.55 (s, 1H), 3.71-3.52 (m, 4H), 1.29-1.22 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 142.3, 139.8, 135.8, 128.7, 126.5, 126.2, 125.6, 124.7, 120.5, 119.8, 101.6, 61.2, 15.3; IR (neat) 3102, 2973, 2927, 2879, 1701, 1612, 1442, 1333, 1176, 1051, 772; HRMS (ESI) calcd for $C_{13}H_{12}OS$: 216.0609, found 217.0688 $(M+H)^+$.

6-(3-Formylphenyl)nicotinaldehyde (7a). The general procedure was followed on a 0.35 mmol scale starting from 6-chloronicotinaldehyde **6a**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **7a** as a white solid (27 mg, 37%): R_f 0.29 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.15 (s, 1H), 10.12 (s, 1H), 9.15 (d, J = 1.4 Hz, 1H), 8.58 (s, 1H), 8.37 (dt, J = 7.8, 1.2 Hz, 1H), 8.26 (dd, J = 8.2, 2.1 Hz, 1H), 8.00-7.96 (m, 2H), 7.68 (t, J = 7.7 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 191.9, 190.3, 160.6, 152.4, 138.9, 137.1, 136.9, 133.3, 131.2, 130.4, 129.8, 128.8, 120.8; IR (neat) 3053, 2852, 2745, 1689, 1587, 1359, 1212, 1183, 1166, 835, 795, 740; HRMS (ESI) calcd for $C_{13}H_9NO_2$: 211.0633, found 212.0708 $(M+H)^+$.

5-Methyl-2-(3-vinylphenyl)pyrimidine (9a). The general procedure was followed on a 0.34 mmol scale starting from 2-chloro-5-methylpyrimidine **8a**. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford **9a** as a yellow oil (14 mg, 21%): R_f 0.60 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.65 (d, J = 5.1 Hz, 1H), 8.48 (t, J = 1.9 Hz, 1H), 8.34 (dt, J = 7.7, 1.5 Hz, 1H), 7.54 (dt, J = 7.7, 1.6 Hz, 1H), 7.45 (t, J = 7.7 Hz, 1H), 7.05 (d, J = 5.0 Hz, 1H), 6.82 (dd, J = 17.6, 10.9 Hz, 1H), 5.87 (dd, J = 17.4, 0.9 Hz, 1H), 5.30 (dd, J = 10.8, 0.9 Hz, 1H), 2.60 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.3, 164.2, 156.2, 138.1, 137.9, 136.7, 128.8, 128.2, 127.6, 126.2, 118.7, 114.3, 24.5; IR (neat) 3061, 3038, 2954, 2928, 1692, 1572, 1555, 1431, 1384, 912, 789; HRMS (ESI) calcd for $C_{13}H_{12}N_2$: 196.1000, found 197.1080 $(M+H)^+$.

2-(4-(6-(Dimethylamino)pyrazin-2-yl)phenyl)propan-2-ol (11a). The general procedure was followed on a 0.32 mmol scale starting from 6-chloro-*N*,*N*-dimethylpyrazin-

2-amine **10a**. The crude material was purified on silica gel (40% EtOAc/hexanes) to afford **11a** as a yellow solid (34 mg, 41%): R_f 0.08 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.96 (d, *J* = 8.4 Hz, 2H), 7.91 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 3.17 (s, 6H), 2.37 (s(br), 1H), 1.61 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 154.3, 150.4, 149.1, 135.9, 128.3, 127.8, 126.7, 124.9, 72.5, 37.5, 31.8; IR (neat) 3371, 3059, 2971, 2923, 2869, 1583, 1566, 1527, 1425, 1402, 1186, 1151, 996, 831; HRMS (ESI) calcd for $C_{15}H_{19}N_3O$: 257.1528, found 258.1603 $(M+H)^+$.

1-(3-(6-Phenylpyridazin-3-yl)phenyl)ethanone (13a). The general procedure was followed on a 0.26 mmol scale starting from 3-chloro-6-phenylpyridazine **12a**. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford **13a** as a yellow solid (18 mg, 25%): R_f 0.25 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.75 (t, *J* = 1.9 Hz, 1H), 8.39 (dt, *J* = 7.9, 1.4 Hz, 1H), 8.16 (dd, *J* = 8.1, 2.1 Hz, 2H), 8.09 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.99 (q, *J* = 7.1 Hz, 2H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.59-7.51 (m, 3H), 2.71 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 197.9, 158.0, 156.7, 137.8, 136.6, 135.8, 131.3, 130.3, 129.7, 129.4, 129.1, 126.9, 126.8, 124.4, 124.3, 26.9; IR (neat) 3061, 3000, 2932, 1683, 1601, 1585, 1432, 1398, 1358, 1236, 689; HRMS (ESI) calcd for $C_{18}H_{14}N_2O$: 274.1106, found 275.1191 $(M+H)^+$.

Compounds **39-41** were prepared according to the following procedure: **Method A**: In a sealed tube, the triarylbismuthine (1.0 equiv.) was added, followed by copper (II) acetate (0.1 equiv.) and the azole or diazole (1.0 equiv.). The reagents were dissolved in anhydrous dichloromethane (4 mL) and pyridine (1.0 equiv.) was added to the mixture. The reaction tube was purged with dry oxygen for 30 seconds, sealed and heated at 50°C overnight. The reaction mixture was cooled to r.t., transferred and rinsed with EtOAc in a round bottom flask. Silica gel was added and the mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using EtOAc/hexanes as the eluent to give the corresponding product. **Method B**: Idem as method **A** except for copper (II) acetate (1.0 equiv. instead of 0.1 equiv.) and pyridine (3.0 equiv. instead of 1.0 equiv.).

1-(4-((Tetrahydro-*2H*-pyran-2-yl)oxy)phenyl)-*1H*-indole-5-carbaldehyde (39a). Method B was followed on a 0.17 mmol scale starting from *1H*-indole-5-carbaldehyde **36**. The crude product was purified on silica gel (15% EtOAc/hexanes) to afford **39a** as a yellow solid (43 mg, 79%): R_f 0.52 (20% EtOAc/hexanes); ^{1}H-NMR (300

MHz, $CDCl_3$) δ 10.04 (s, 1H), 8.19 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 3.0 Hz, 1H), 5.49 (s, 1H), 3.98-3.91 (m, 1H), 3.65 (d, *J* = 11.4 Hz, 1H), 2.07-1.99 (m, 1H), 1.92-1.90 (m, 2H), 1.76-1.58 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 192.4, 156.4, 139.6, 132.6, 130.4, 139.9, 128.8, 126.4, 126.1, 122.5, 117.5, 111.1, 104.8, 96.7, 62.2, 30.4, 25.2, 18.7; IR (neat) 3101, 3039, 2943, 2873, 2850, 2715, 1683, 1615, 1509, 1330, 1237, 1201, 1102, 921, 731; HRMS (ESI) calcd for $C_{20}H_{19}NO_3$: 321.1365, found 322.1430 $(M+H)^+$.

1-(2-Formylphenyl)-*1H*-indole-5-carbaldehyde (39b). Method B was followed on a 0.17 mmol scale starting from *1H*-indole-5-carbaldehyde **36**. The crude product was purified on silica gel (20% EtOAc/hexanes) to afford **39b** as a yellow oil (15 mg, 35%): R_f 0.44 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.07 (s, 1H), 9.63 (s, 1H), 8.25 (d, *J* = 1.0 Hz, 1H), 8.12 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.83-7.76 (m, 2H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.51 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.39 (d, *J* = 3.3 Hz, 1H), 7.23 (s, 1H), 6.91 (dd, *J* = 3.3, 0.6 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 192.2, 188.9, 141.4, 140.9, 135.3, 132.2, 131.8, 131.6, 130.6, 129.2, 128.6, 128.3, 126.3, 123.5, 110.8, 105.9; IR (neat) 3106, 3065, 2977, 2920, 2867, 2745, 1687, 1597, 1490, 1331, 1195; HRMS (ESI) calcd for $C_{16}H_{11}NO_2$: 249.0790, found 250.0873 $(M+H)^+$.

1-(3-(Hydroxymethyl)phenyl)-*1H*-indole-5-carbaldehyde (39c). Method A was followed on a 0.22 mmol scale starting from *1H*-Indole-5-carbaldehyde **36**. The crude product was purified on silica gel (30% EtOAc/hexanes) to afford **39c** as a yellow oil (34 mg, 62%): R_f 0.15 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.03 (s, 1H), 8.19 (d, *J* = 1.1 Hz, 1H), 7.75 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.53-7.51 (m, 2H), 7.42-7.40 (m, 3H), 6.81 (d, *J* = 3.3 Hz, 1H), 4.82 (s, 2H), 2.22 (s(br), 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 192.4, 143.1, 139.2, 130.1, 130.0, 129.9, 129.1, 126.4, 125.7, 123.7, 122.9, 122.8, 111.2, 105.4, 105.3, 64.7; IR (neat) 3411, 3105, 3055, 2920, 2858, 2815, 2727, 1682, 1589, 1493, 1449, 1331, 1223, 1103, 1032, 726, 698; HRMS (ESI) calcd for $C_{16}H_{13}NO_2$: 251.0946, found 252.1012 $(M+H)^+$.

1-(3-Acetylphenyl)-*1H*-indole-5-carbaldehyde (39d). Method B was followed on a 0.17 mmol scale starting from *1H*-indole-5-carbaldehyde **36**. The crude product was purified on silica gel (30% EtOAc/hexanes) to afford **39d** as a yellow oil (27 mg, 60%): R_f 0.34 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.18 (d, *J* = 16.5 Hz,

1H), 8.08 (s, 1H), 7.99 (d, *J* = 7.3 Hz, 1H), 7.81-7.64 (m, 3H), 7.56 (d, *J* = 8.6 Hz, 1H), 7.49-7.44 (m, 1H), 6.86 (d, *J* = 3.3 Hz, 1H), 2.67 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 197.2, 192.4, 139.4, 139.1, 138.7, 130.3, 129.8, 129.2, 128.9, 127.3, 126.5, 124.1, 123.1, 111.8, 110.9, 105.9, 26.9; IR (neat) 3103, 3057, 2924, 2825, 2741, 1682, 1599, 1586, 1491, 1445, 1330, 1236, 1105, 769; HRMS (ESI) calcd for $C_{17}H_{13}NO_2$: 263.0946, found 264.1012 $(M+H)^+$.

1-(1-(3-(1-Hydroxyethyl)phenyl)-*1H*-pyrrol-2-yl)ethanone (40a). Method B was followed on a 0.46 mmol scale starting from 1-(*1H*-pyrrol-2-yl)ethanone **37**. The crude product was purified on silica gel (35% EtOAc/hexanes) to afford **40a** as a yellow oil (100 mg, 95%): R_f 0.19 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34-7.31 (m, 2H), 7.27-7.26 (m, 1H), 7.12-7.08 (m, 2H), 6.94 (t, *J* = 2.2 Hz, 1H), 6.28 (q, *J* = 4.1 Hz, 1H), 4.84 (q, *J* = 12.9 Hz, 1H), 3.50 (s(br), 1H), 2.37 (s, 3H), 1.45 (d, *J* = 6.5 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 187.5, 147.1, 140.9, 131.5, 131.4, 128.6, 124.9, 124.7, 123.4, 120.9, 109.3, 69.6, 27.2, 25.1; IR (neat) 3409, 3114, 3057, 2973, 2920, 2867, 2243, 1644, 1405, 1084, 940, 793, 738; HRMS (ESI) calcd for $C_{14}H_{15}NO_2$: 229.1103, found 481.2106 $(2M+Na)^+$.

3-Methyl-1-(3-vinylphenyl)-*1H*-pyrazole (40b). Method B was followed on a 0.37 mmol scale starting from 3-methyl-*1H*-pyrazole **37**. The crude product was purified on silica gel (20% EtOAc/hexanes) to afford **40b** as a yellow oil (40 mg, 59%): R_f 0.53 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 2.4 Hz, 1H), 7.71 (t, *J* = 2.0 Hz, 1H), 7.50 (dq, *J* = 7.9, 1.3 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.29 (dt, *J* = 7.5, 1.5 Hz, 1H), 6.75 (dd, *J* = 17.6, 10.8 Hz, 1H), 6.25 (d, *J* = 2.4 Hz, 1H), 5.83 (dd, *J* = 17.6, 0.75 Hz, 1H), 5.32 (d, *J* = 11.3 Hz, 1H), 2.39 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 150.6, 139.0, 136.2, 129.5, 127.5, 123.8, 121.4, 118.1, 116.8, 115.1, 107.6, 13.8; IR (neat) 3141, 3118, 3065, 2926, 2863, 1695, 1606, 1585, 1533, 1489, 1454, 1362, 1047, 755; HRMS (ESI) calcd for $C_{12}H_{12}N_2$: 184.1000, found 185.1078 $(M+H)^+$.

(*E*)-Ethyl 3-(3-(3-cyano-2-oxopyridin-1(*2H*)-yl)phenyl)acrylate (41a). Method B was followed on a 0.093 mmol scale starting from 2-oxo-1,2-dihydropyridine-3-carbonitrile **38**. The crude product was purified on silica gel (50% EtOAc/hexanes) to afford **41a** as a white solid (18 mg, 66%): R_f 0.07 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 7.1, 2.1 Hz, 1H), 7.71-7.69 (m, 1H), 7.63-7.59 (m, 2H), 7.53-7.51 (m, 2H), 7.38 (dt, *J* = 7.7, 1.6 Hz, 1H), 6.45 (d, *J* = 16.0 Hz, 1H), 6.38 (t, *J* = 6.9 Hz, 1H), 4.25 (q, *J* = 14.2 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.4, 159.2, 147.9, 142.8, 142.5, 140.0,

136.3, 130.2, 128.9, 127.6, 125.5, 120.4, 115.2, 106.9, 105.7, 60.8, 14.3; IR (neat) 3080; 2977, 2924, 2905, 2228, 1707, 1662, 1542, 1269, 1181; HRMS (ESI) calcd for $C_{17}H_{14}N_2O_3$: 294.1004, found 295.1099 $(M+H)^+$.

Compounds **44** were prepared according to the following procedure: **Method A**: In a sealed tube, the phenol (1.0 equiv.) was dissolved in non-anhydrous solvent grade dichloromethane (3 mL). The organobismuthane (1.0 equiv.) was added followed by copper (II) acetate (1.0 equiv.) and Et_3N (3.0 equiv.). The tube was sealed and heated at 50°C during 3h. The reaction mixture was cooled to r.t. and silica gel was added. The mixture was concentrated under reduced pressure and the crude product was purified by flash column chromatography using the indicated solvent system. The pure fractions were concentrated under reduced pressure to afford the desired pure product. **Method B**: Idem as method **A** except for $Cu(OAc)_2$ (0.3 equiv.) under O_2 during 16h.

Methyl 3-(3-(diethoxymethyl)phenoxy)benzoate (44a). Method B was followed on a 0.16 mmol scale starting from methyl 3-hydroxybenzoate **43**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **44a** as a colorless oil (32 mg, 61%): R_f 0.62 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.79 (dt, J = 7.7, 1.3 Hz, 1H), 7.67 (t, J = 2.5 Hz, 1H), 7.45-7.34 (m, 2H), 7.30-7.21 (m, 2H), 7.18 (t, J = 2.1 Hz, 1H), 6.96 (dq, J = 7.9, 1.2 Hz, 1H), 5.50 (s, 1H), 3.91 (s, 3H), 3.69-3.50 (m, 4H), 1.25 (t, J = 7.0 Hz, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.5, 157.4, 156.7, 141.5, 131.9, 129.8, 129.7, 124.3, 123.3, 122.1, 119.5, 118.9, 117.5, 100.9, 61.1, 52.3, 15.5; IR (neat) 3076, 2975, 2929, 2882, 1772, 1725, 1584, 1484, 1441, 1274, 1208, 1097, 1053, 756; HRMS (ESI) calcd for $C_{19}H_{22}O_5$: 330.1467, found 353.1369 $(M+Na)^+$.

***(E)*-Methyl 3-(3-(3-ethoxy-3-oxoprop-1-en-1-yl)phenoxy)benzoate (44b).** Method B was followed on a 0.16 mmol scale starting from methyl 3-hydroxybenzoate **43**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **44b** as a yellow oil (51 mg, 98%): R_f 0.61 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 7.7 Hz, 1H), 7.69-7.67 (m, 1H), 7.62 (s, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.29 (d, J = 9.5 Hz, 1H), 7.24 (dt, J = 8.1, 0.8 Hz, 1H), 7.17 (d, J = 1.7 Hz, 1H), 7.04 (dd, J = 7.9, 0.8 Hz, 1H), 6.39 (d, J = 16.0 Hz, 1H), 4.27 (q, J = 14.3 Hz, 2H), 3.92 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.8, 166.4, 157.4, 156.9, 143.7, 136.5, 132.1, 130.4, 129.9, 124.8, 123.6, 123.5, 120.6, 119.9, 119.2, 117.9, 60.6, 52.3, 14.3; IR (neat) 3065, 2980,

2953, 2901, 1709, 1639, 1575, 1484, 1442, 1269, 1230, 1177, 1097, 1036, 983, 756; HRMS (ESI) calcd for $C_{19}H_{18}O_5$: 326.1154, found 327.1224 $(M+H)^+$.

Methyl 3-(3-vinylphenoxy)benzoate (44c). Method B was followed on a 0.13 mmol scale starting from methyl 3-hydroxybenzoate **43**. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford **44c** as a yellow oil (27 mg, 82%): R_f 0.74 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 7.7 Hz, 1H), 7.67 (t, J = 1.9 Hz, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 7.23-7.17 (m, 2H), 7.07 (s, 1H), 6.90 (dd, J = 8.0, 1.6 Hz, 1H), 6.68 (dd, J = 17.6, 10.9 Hz, 1H), 5.73 (d, J = 17.6 Hz, 1H), 5.27 (d, J = 10.9 Hz, 1H), 3.90 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.5, 157.4, 156.9, 139.7, 136.2, 131.9, 129.9, 129.8, 124.4, 123.3, 121.8, 119.6, 118.5, 116.7, 114.9, 52.3; IR (neat) 3076, 3008, 2952, 2928, 2844, 1724, 1573, 1485, 1442, 1275, 1250, 1208, 1143, 1098; HRMS (ESI) calcd for $C_{16}H_{14}O_3$: 254.0943, found 255.1010 $(M+H)^+$.

Methyl 4-(2-(diethoxymethyl)phenoxy)benzoate (44d). Method A was followed on a 0.23 mmol scale starting from methyl 3-hydroxybenzoate **43**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **44d** as a colorless oil (38 mg, 50%): R_f 0.73 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.78-7.72 (m, 2H), 7.64 (t, J = 2.0 Hz, 1H), 7.42-7.28 (m, 2H), 7.24-7.15 (m, 2H), 6.91 (d, J = 8.0 Hz, 1H), 5.76 (s, 1H), 3.91 (s, 3H), 3.70-3.62 (m, 2H), 3.59-3.49 (m, 2H), 1.18 (t, J = 7.0 Hz, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.6, 158.1, 153.7, 131.8, 131.1, 129.8, 129.6, 127.9, 124.3, 123.9, 122.5, 119.6, 118.9, 97.5, 62.3, 52.2, 15.1; IR (neat) 3066, 2975, 2877, 1724, 1580, 1482, 1444, 1271, 1230, 1202, 1052, 994, 905, 754; HRMS (ESI) calcd for $C_{19}H_{22}O_5$: 330.1467, found 353.1363 $(M+Na)^+$.

3-(3-Iodophenoxy)benzaldehyde (47). The general procedure was followed on a 0.23 mmol scale starting from 3-iodophenol **45**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **47** as a yellow oil (33 mg, 44%): R_f 0.69 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.64 (dt, J = 7.4, 1.0 Hz, 1H), 7.52-7.46 (m, 3H), 7.37 (t, J = 2.0 Hz, 1H), 7.30-7.26 (m, 1H), 7.09 (t, J = 8.1 Hz, 1H), 6.99 (dq, J = 8.2, 0.9 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 191.4, 157.7, 157.0, 138.3, 133.2, 131.4, 130.7, 128.3, 125.5, 124.9, 118.6, 118.5, 94.5; IR (neat) 3059, 2923, 2827, 2734, 1697, 1572, 1465, 1450, 1243, 846, 781; HRMS (ESI) calcd for $C_{13}H_9IO_2$: 323.9647, found 324.9714 $(M+H)^+$.

3-(5-Iodo-*1H*-indol-1-yl)benzaldehyde (48). The general procedure was followed on 0.12 mmol scale starting from 5-iodo-*1H*-indole **46**. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford **48** as a yellow oil (29 mg, 70%): R_f 0.54 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.09 (s, 1H), 8.03-8.00 (m, 1H), 7.98 (s, 1H), 7.87 (dt, *J* = 7.0, 1.7 Hz, 1H), 7.76-7.68 (m, 2H), 7.52-7.42 (m, 1H), 7.33-7.30 (m, 2H), 6.65 (d, *J* = 3.3 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 191.3, 140.2, 137.9, 134.8, 131.9, 131.1, 130.6, 130.2, 129.8, 128.4, 128.3, 124.2, 112.2, 103.8, 84.3; IR (neat) 3106, 3068, 2958, 2920, 2829, 2734, 1698, 1588, 1487, 1459, 1237, 793; HRMS (ESI) calcd for $C_{15}H_{10}INO$: 346.9807, found 347.9896 $(M+H)^+$.

3'-Hydroxy-[1,1'-biphenyl]-3-carbaldehyde (49). The general procedure was followed on a 0.23 mmol scale starting from 3-iodophenol **45**. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford **49** as a white solid (23 mg, 51%): R_f 0.38 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.06 (s, 1H), 8.08 (t, *J* = 1.6 Hz, 1H), 7.87-7.82 (m, 2H), 7.59 (t, *J* = 7.7 Hz, 1H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.17 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.12 (t, *J* = 2.2 Hz, 1H), 6.90 (dq, *J* = 8.1, 0.8 Hz, 1H), 5.87 (s(br), 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 192.7, 156.2, 141.8, 141.4, 136.9, 133.2, 130.3, 129.6, 128.9, 128.2, 119.7, 115.1, 114.2; IR (neat) 3363, 3062, 2927, 2831, 2734, 1686, 1599, 1588, 1458, 1308, 1212, 1169, 779, 690; HRMS (ESI) calcd for $C_{13}H_{10}O_2$: 198.0681, found 199.0750 $(M+H)^+$.

3-(*1H*-Indol-5-yl)benzaldehyde (50). The general procedure was followed on 0.21 mmol scale starting from 5-iodo-*1H*-indole **46**. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford **50** as a yellow oil (18 mg, 39%): R_f 0.43 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.14-10.13 (m, 1H), 8.34 (s(br), 1H), 8.20-8.17 (m, 1H), 7.97-7.91 (m, 2H), 7.85 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.71-7.60 (m, 1H), 7.51 (s, 2H), 7.31-7.28 (m, 1H), 6.66 (q, *J* = 3.1 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 192.8, 143.5, 136.8, 135.6, 133.4, 133.0, 131.8, 129.4, 128.5, 127.7, 125.2, 121.6, 119.4, 111.6, 103.1; IR (neat) 3414, 3396, 3057, 2825, 2738, 1689, 1599, 1578, 1466, 1424, 1316, 1197, 792; HRMS (ESI) calcd for $C_{15}H_{11}NO$: 221.0841, found 222.0924 $(M+H)^+$.

ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H, ^{13}C, and IR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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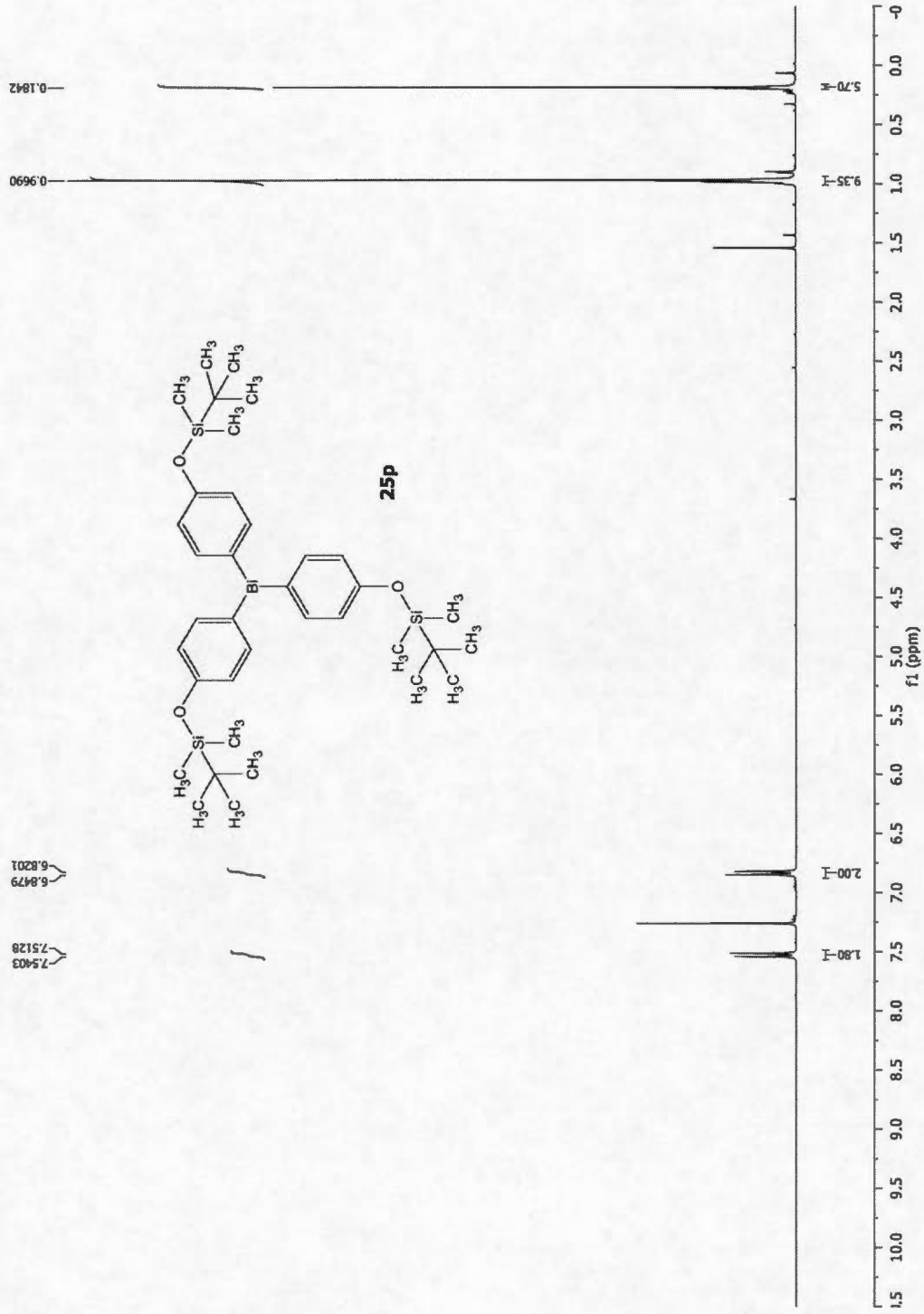
ANNEXE J

"SYNTHESIS OF HIGHLY FUNCTIONNALIZED TRIARYLBISMUTHANES BY FUNCTIONNAL GROUP MANIPULATION AND USE IN *C*–, *N*–, AND *O*–, ARYLATION REACTIONS" SUPPORTING INFORMATION

Article en cours de rédaction

Titre : Synthesis of Highly Functionnalized Triarylbismuthanes by Functionnal Group Manipulation and Use in *C*–, *N*–, and *O*–, Arylation Reactions

Auteurs : Pauline Petiot et Alexandre Gagnon*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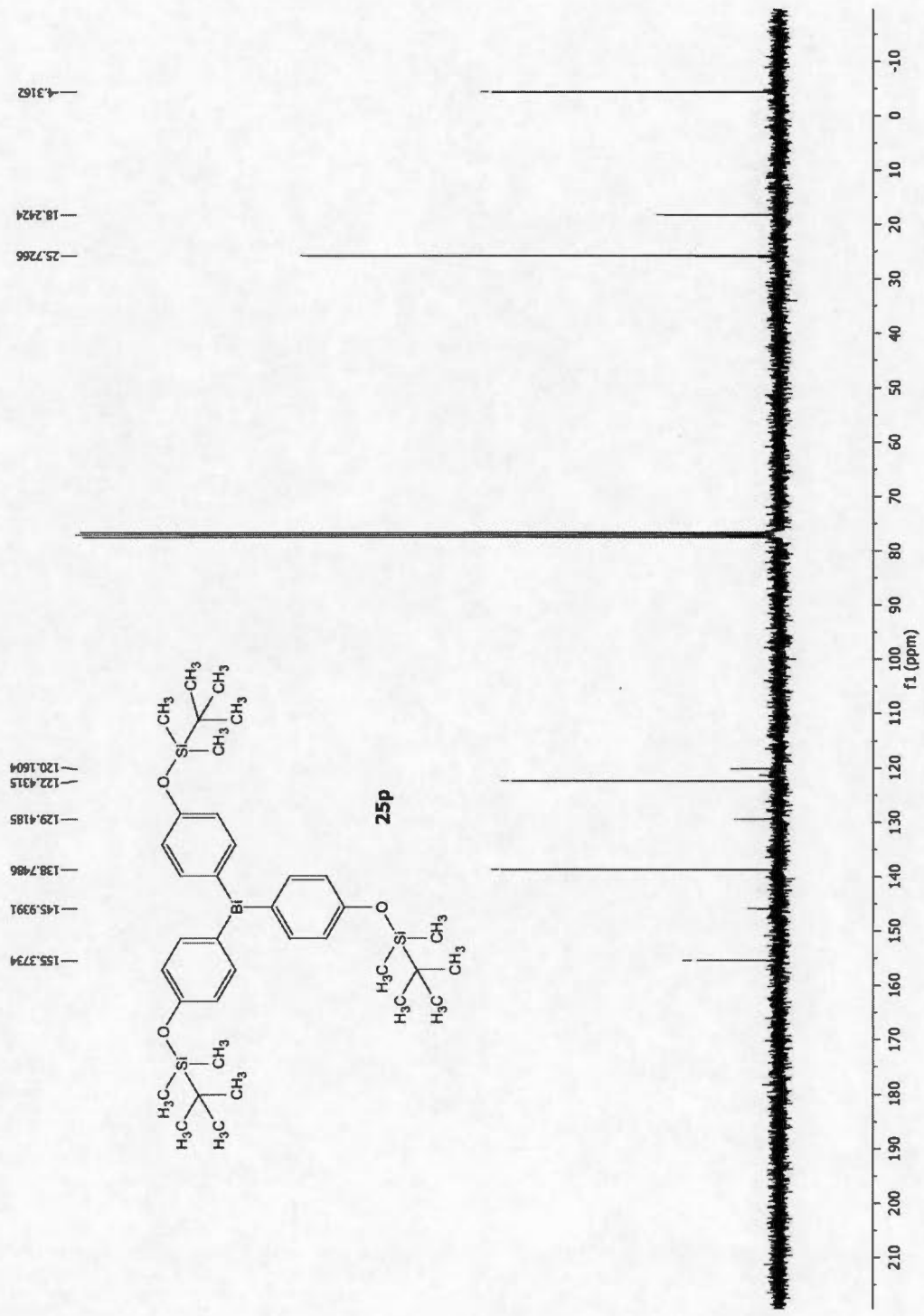
1.80-1
f1 (ppm)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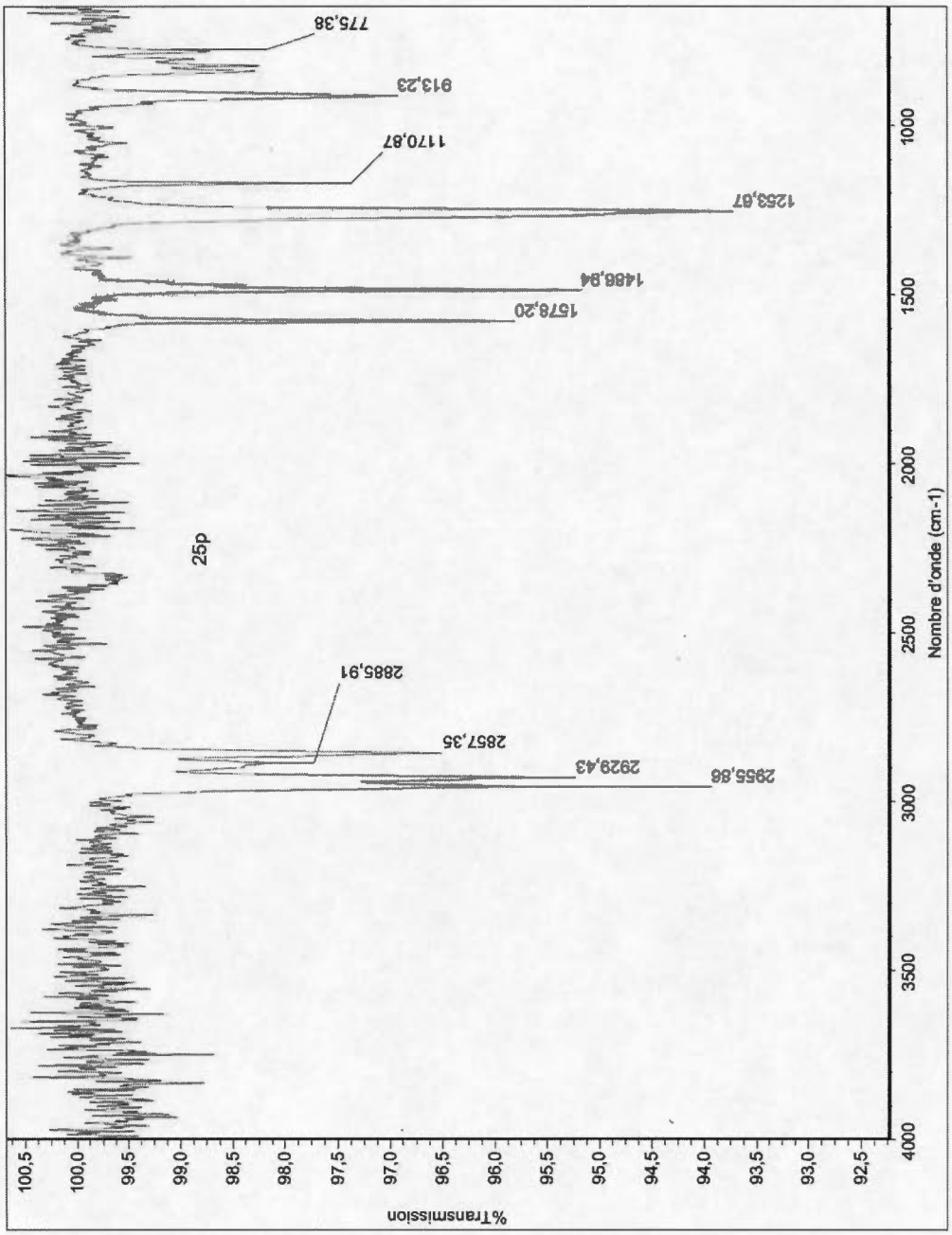
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92,5
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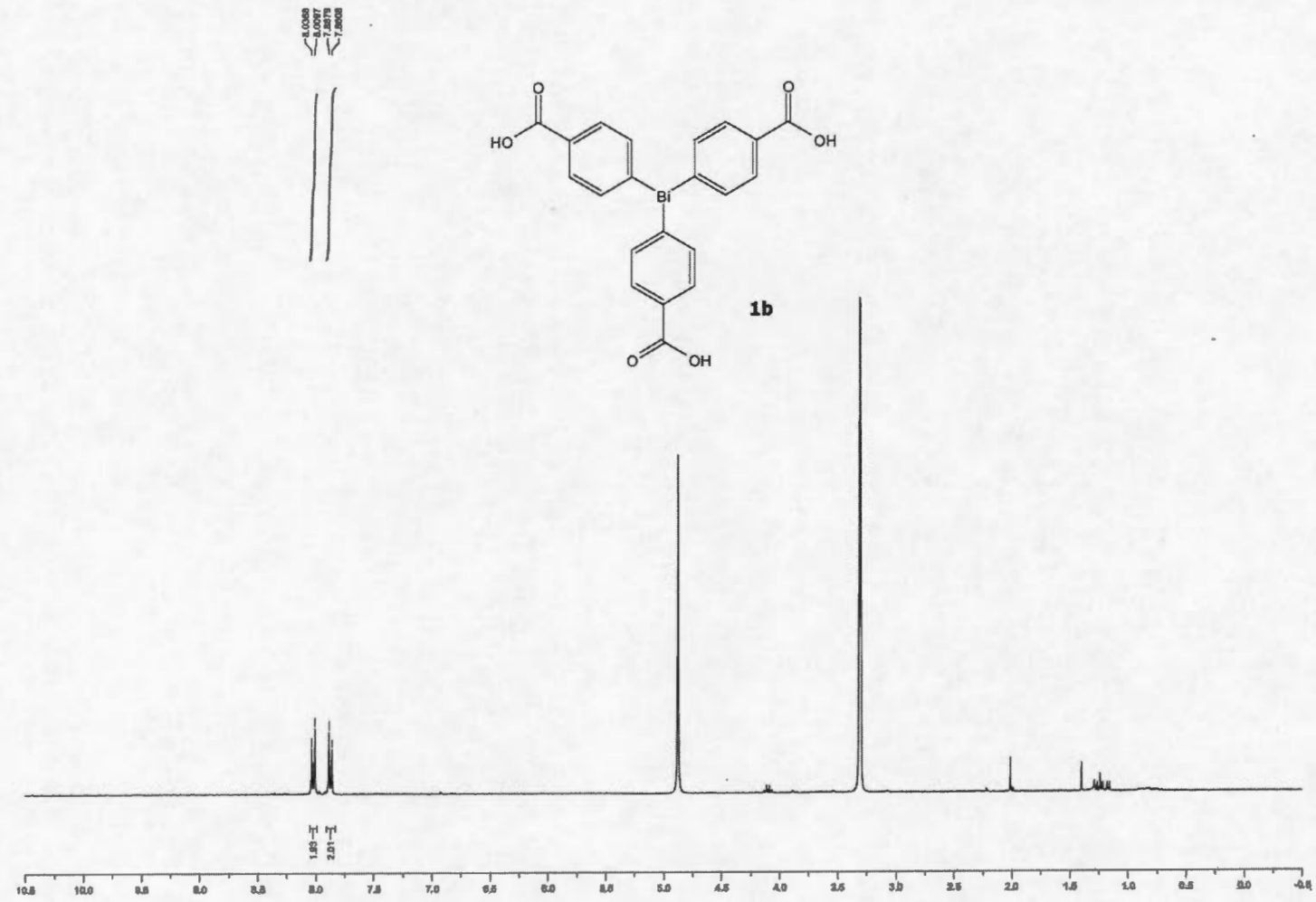
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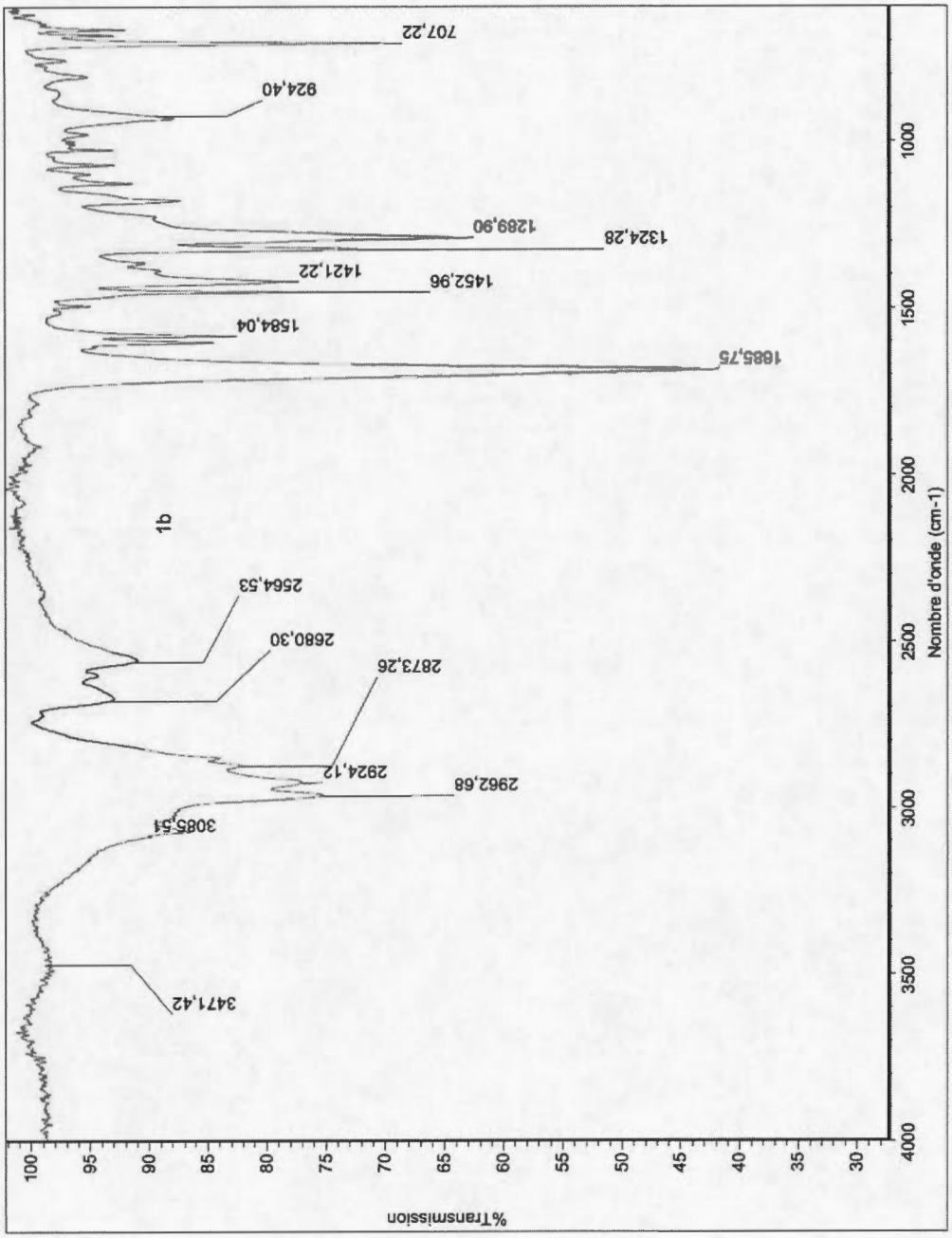
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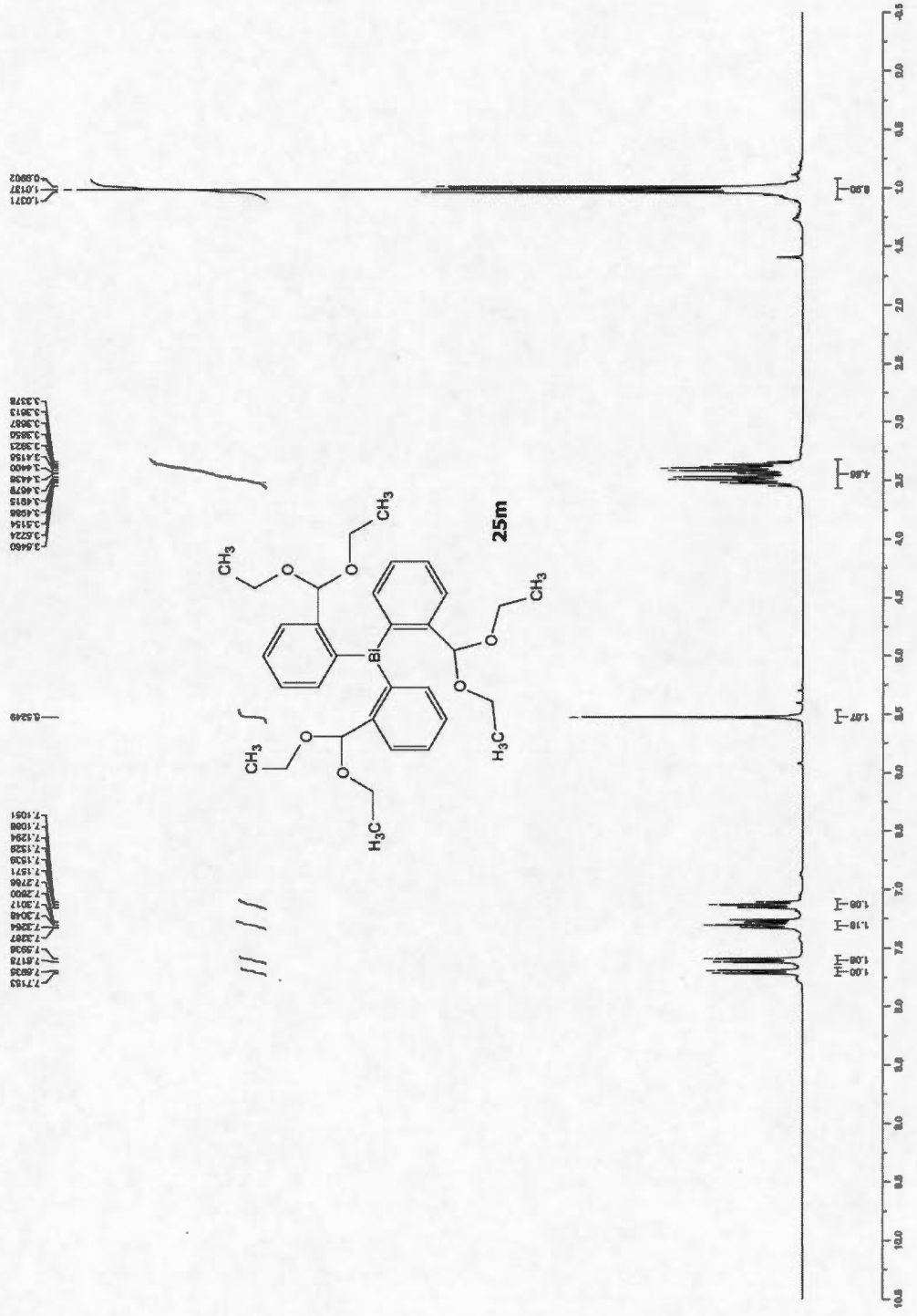
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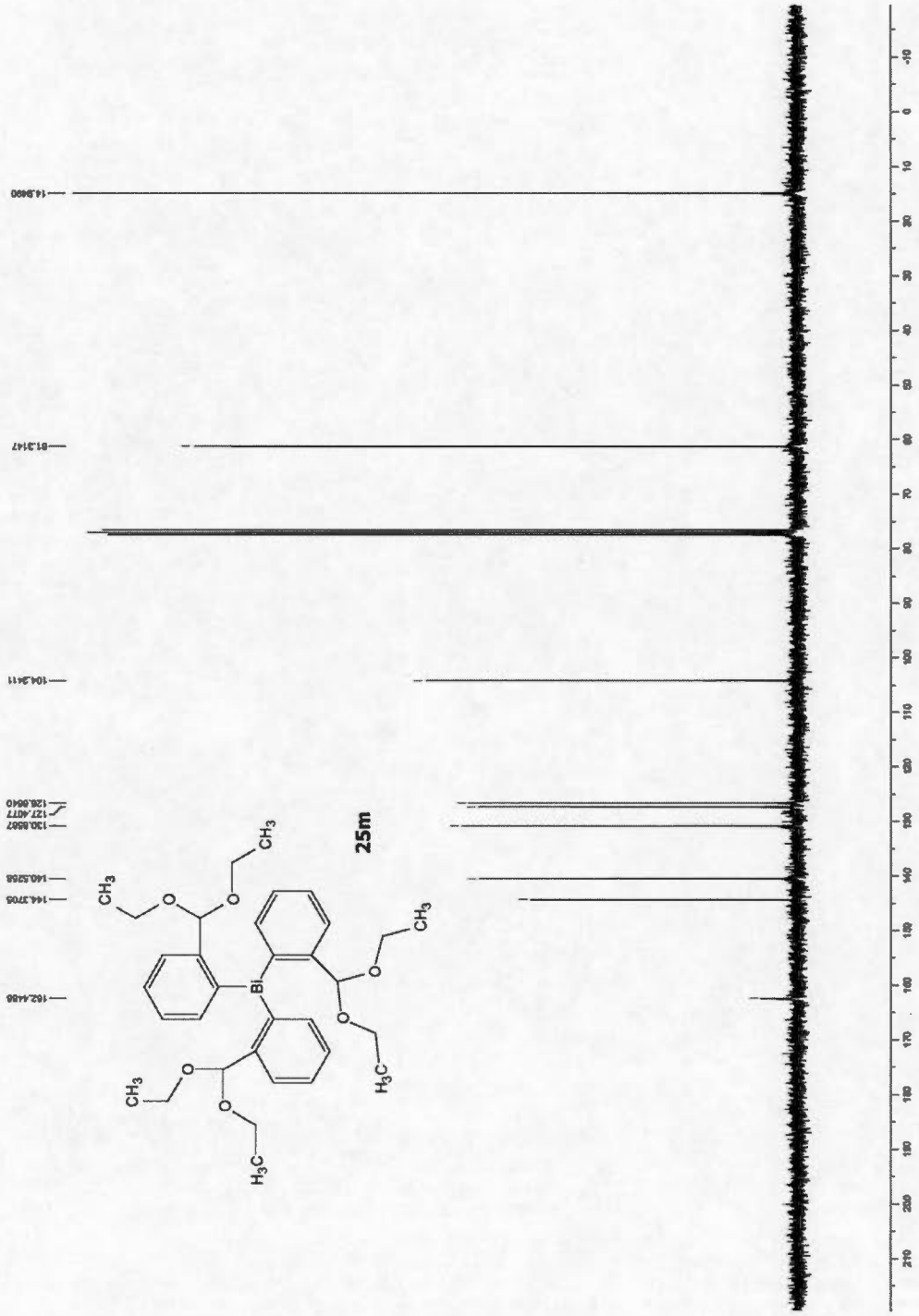
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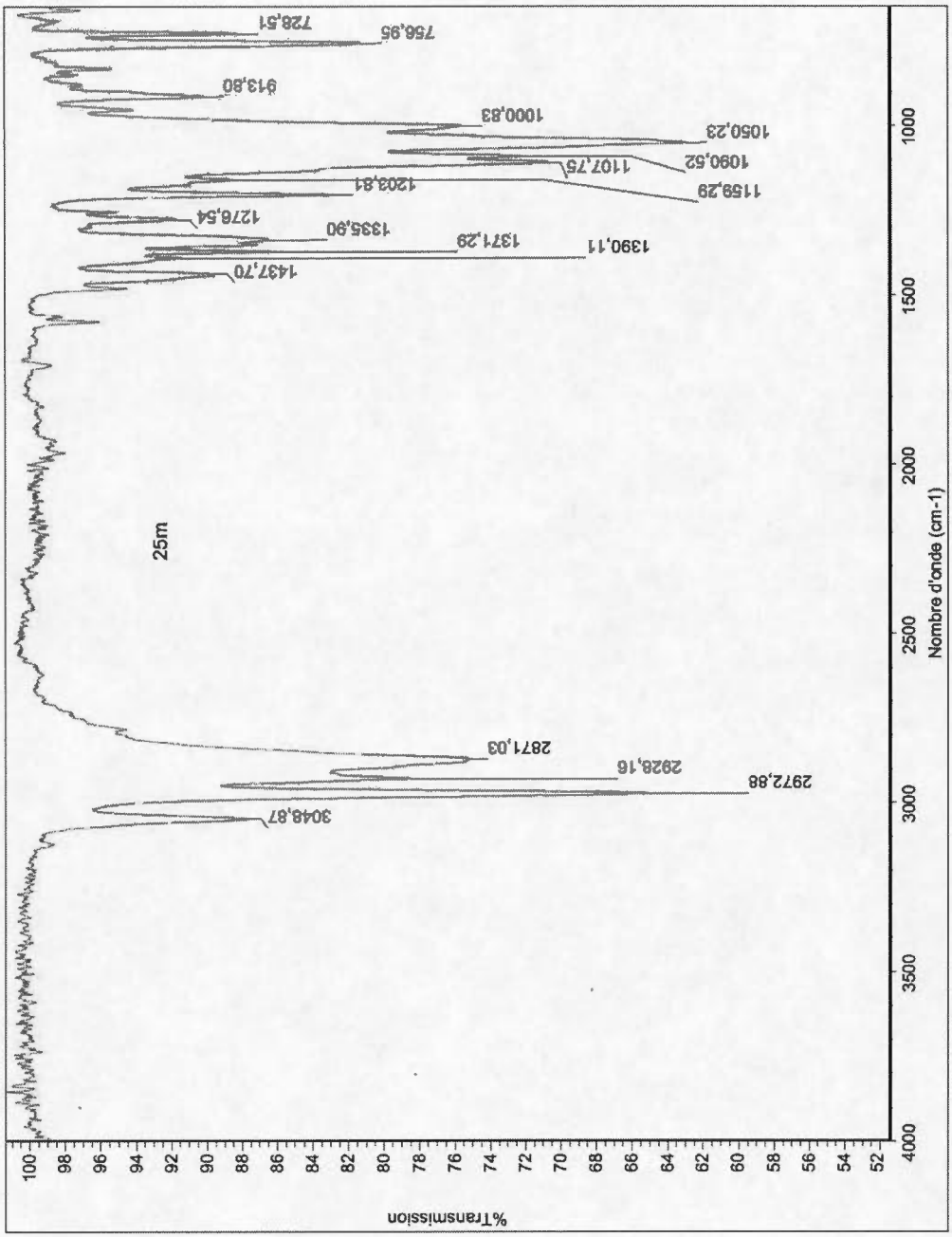
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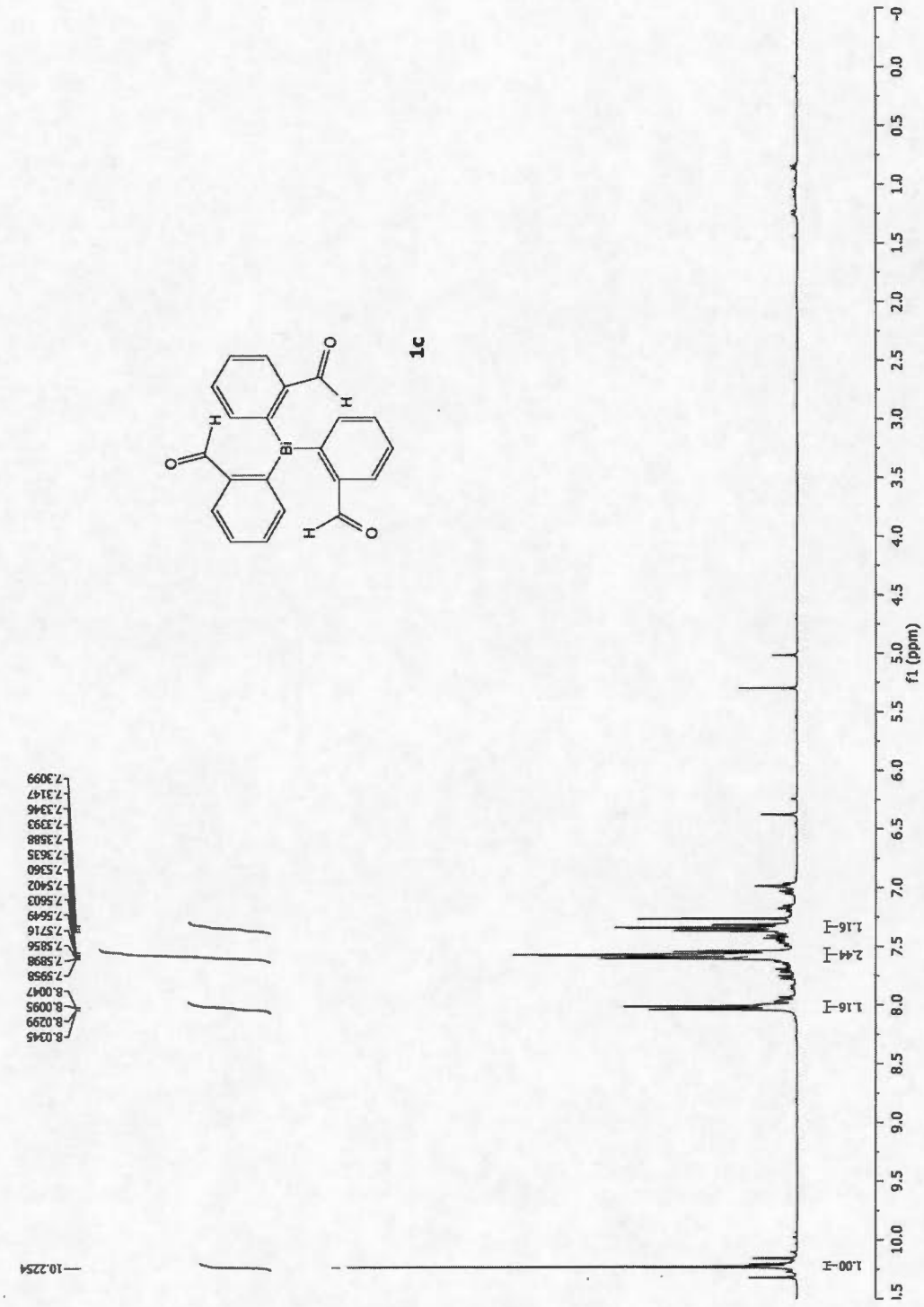
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1.16
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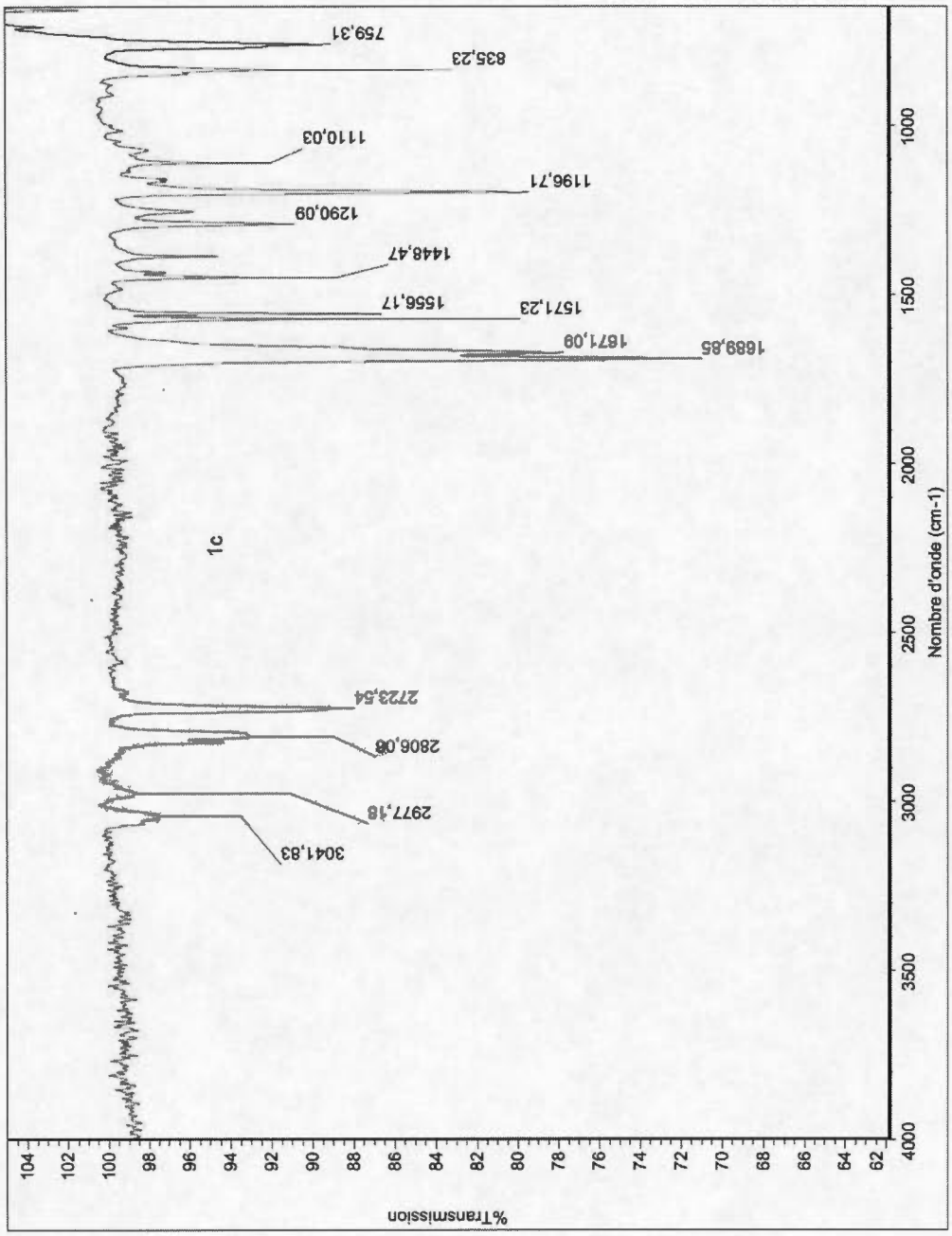
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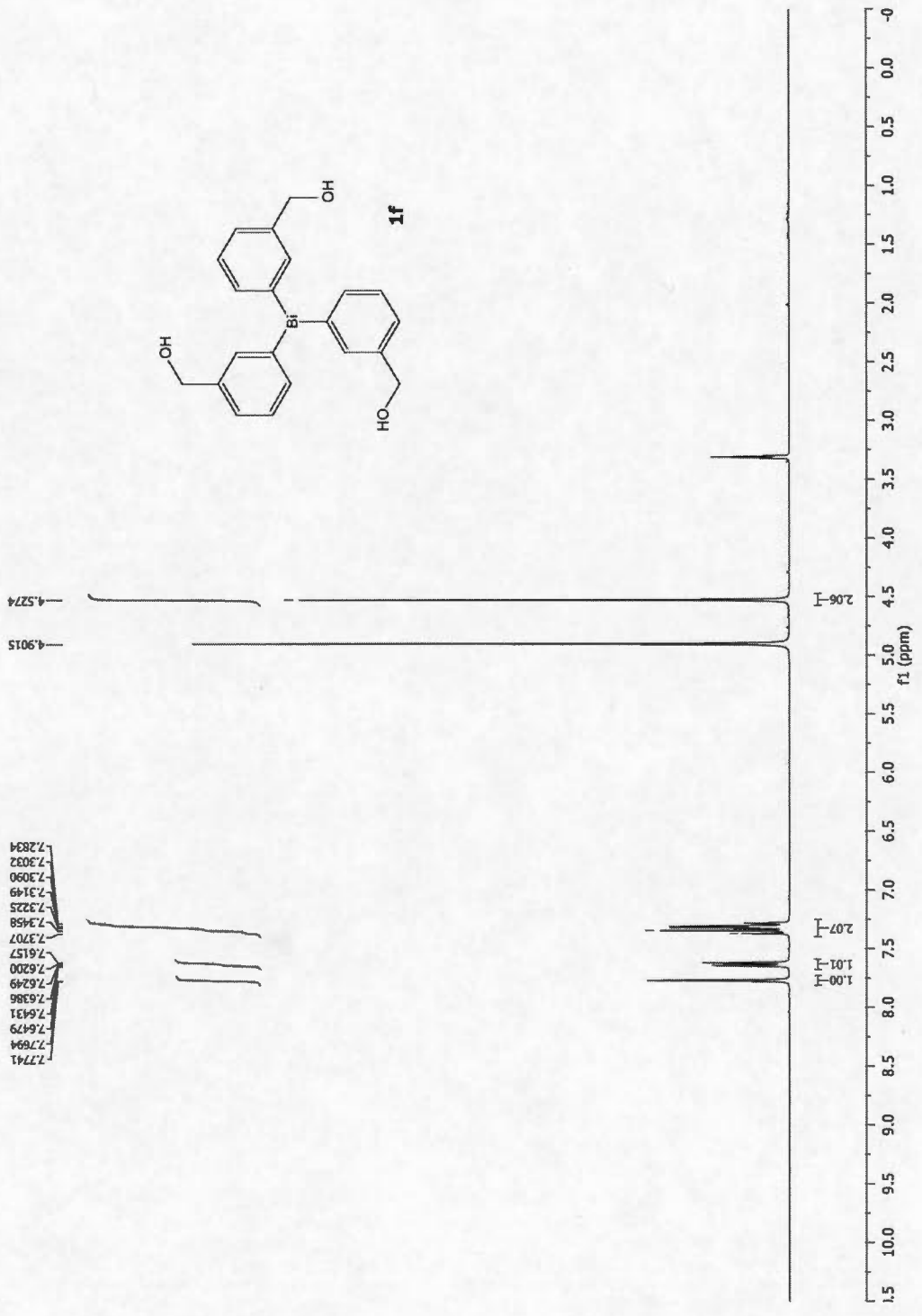
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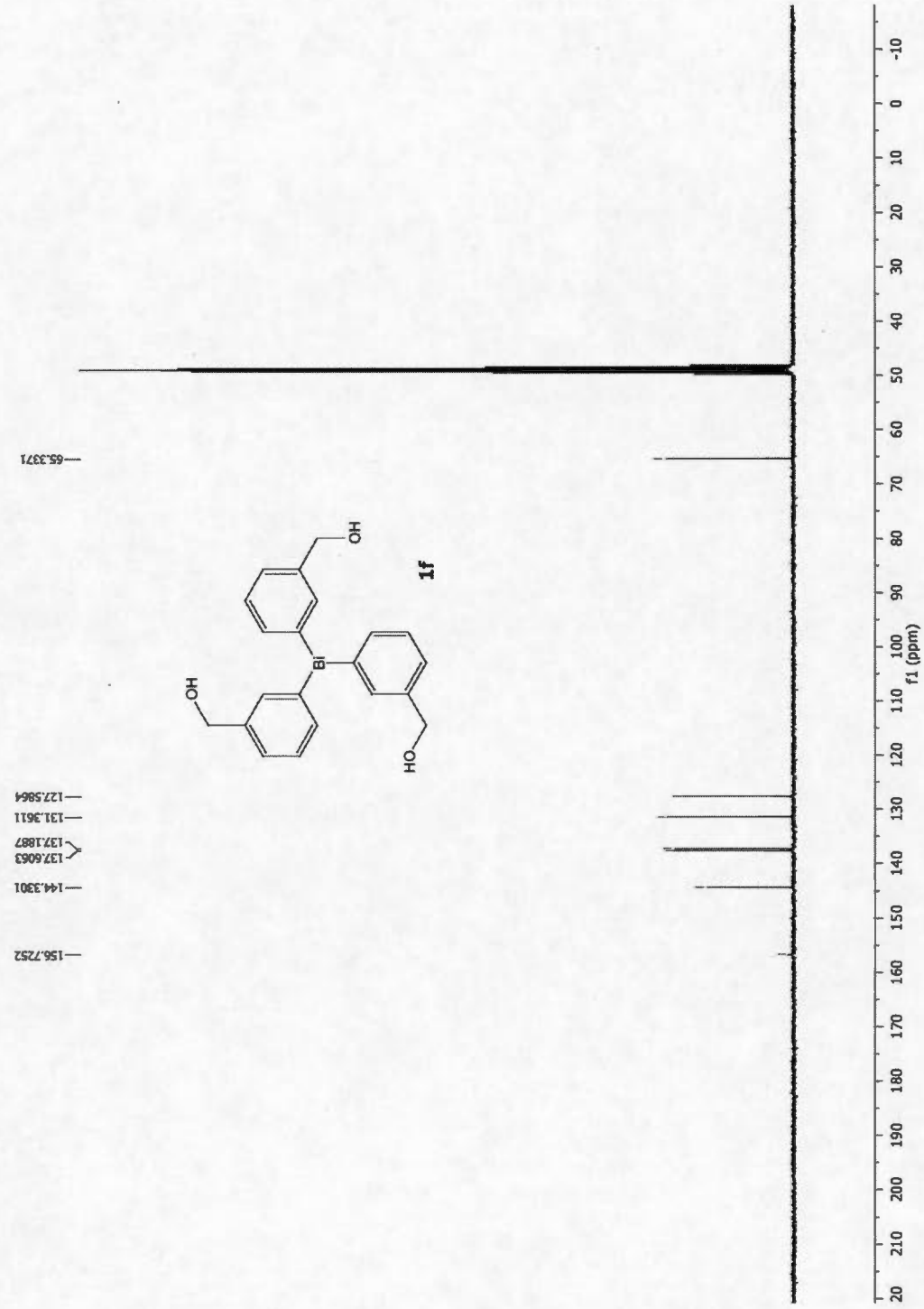
f1 (ppm)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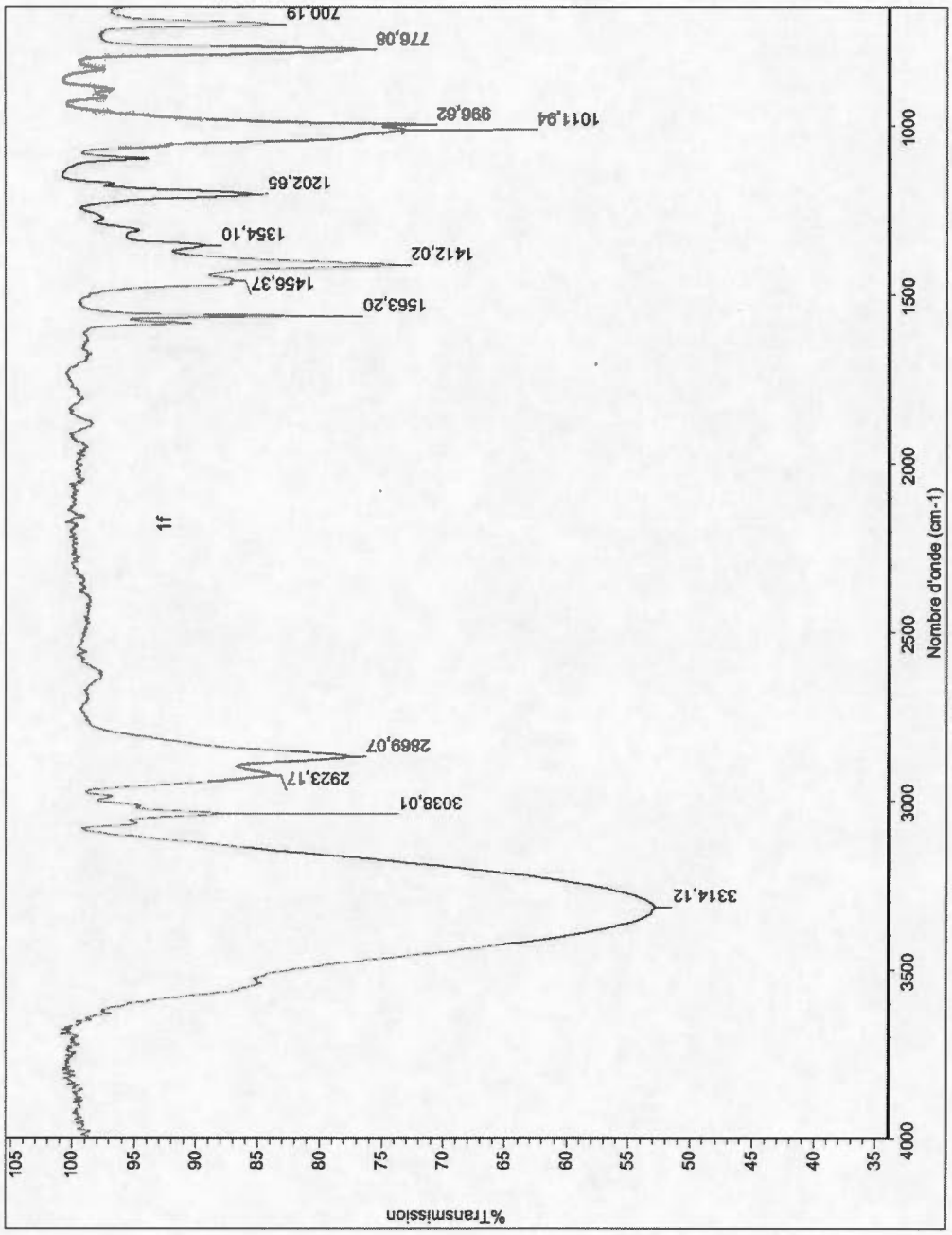
f1 (ppm)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776,08
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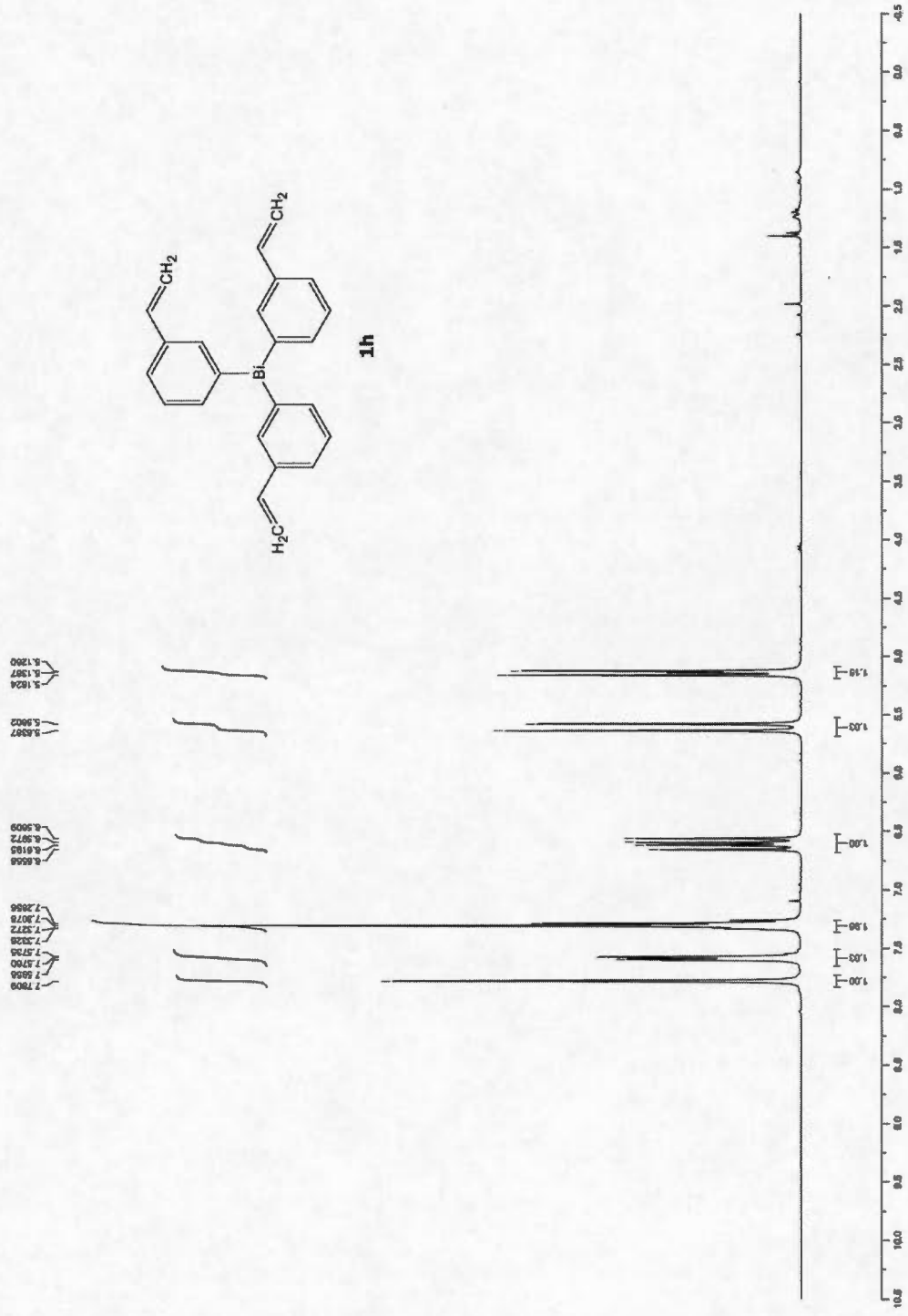
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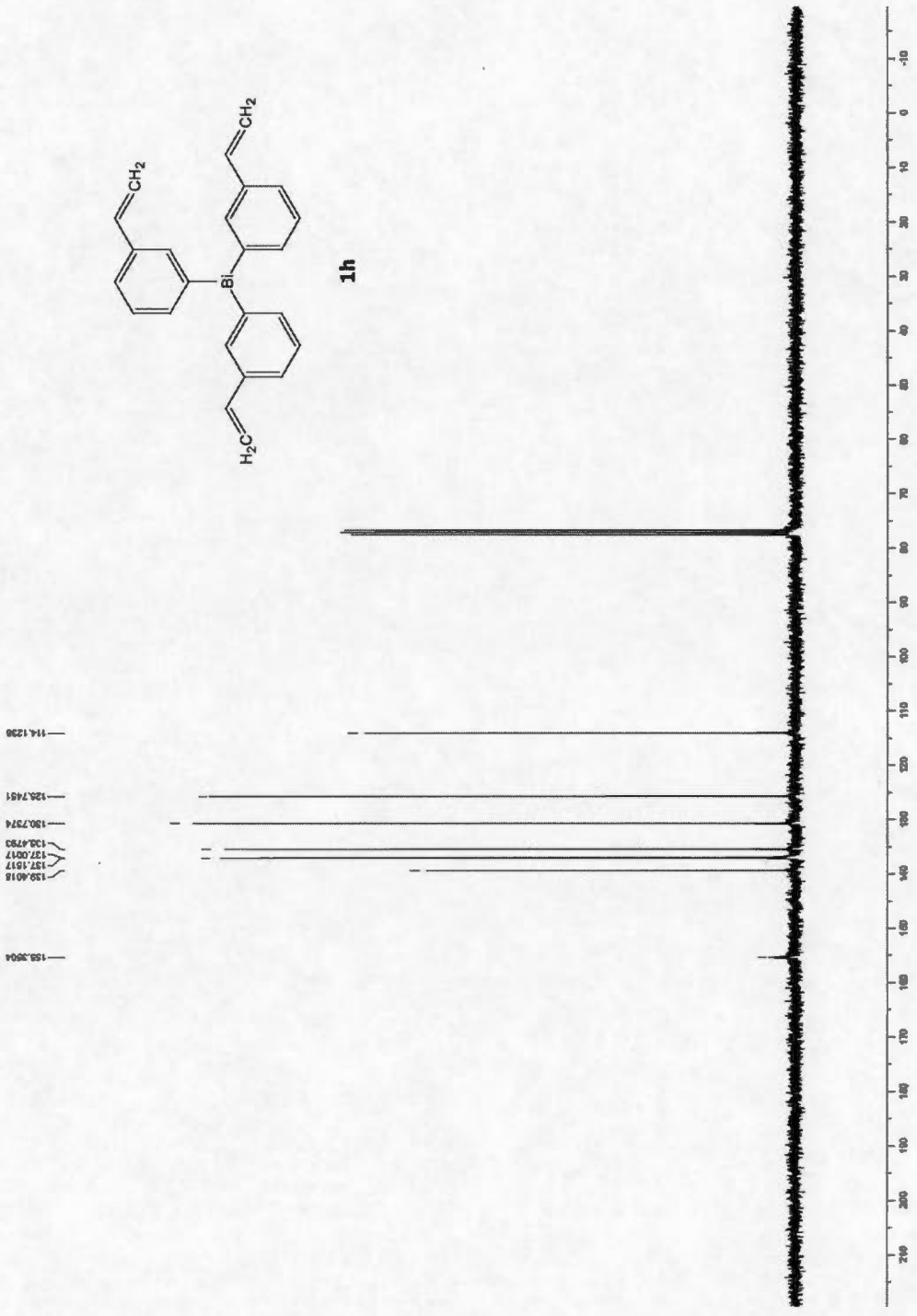
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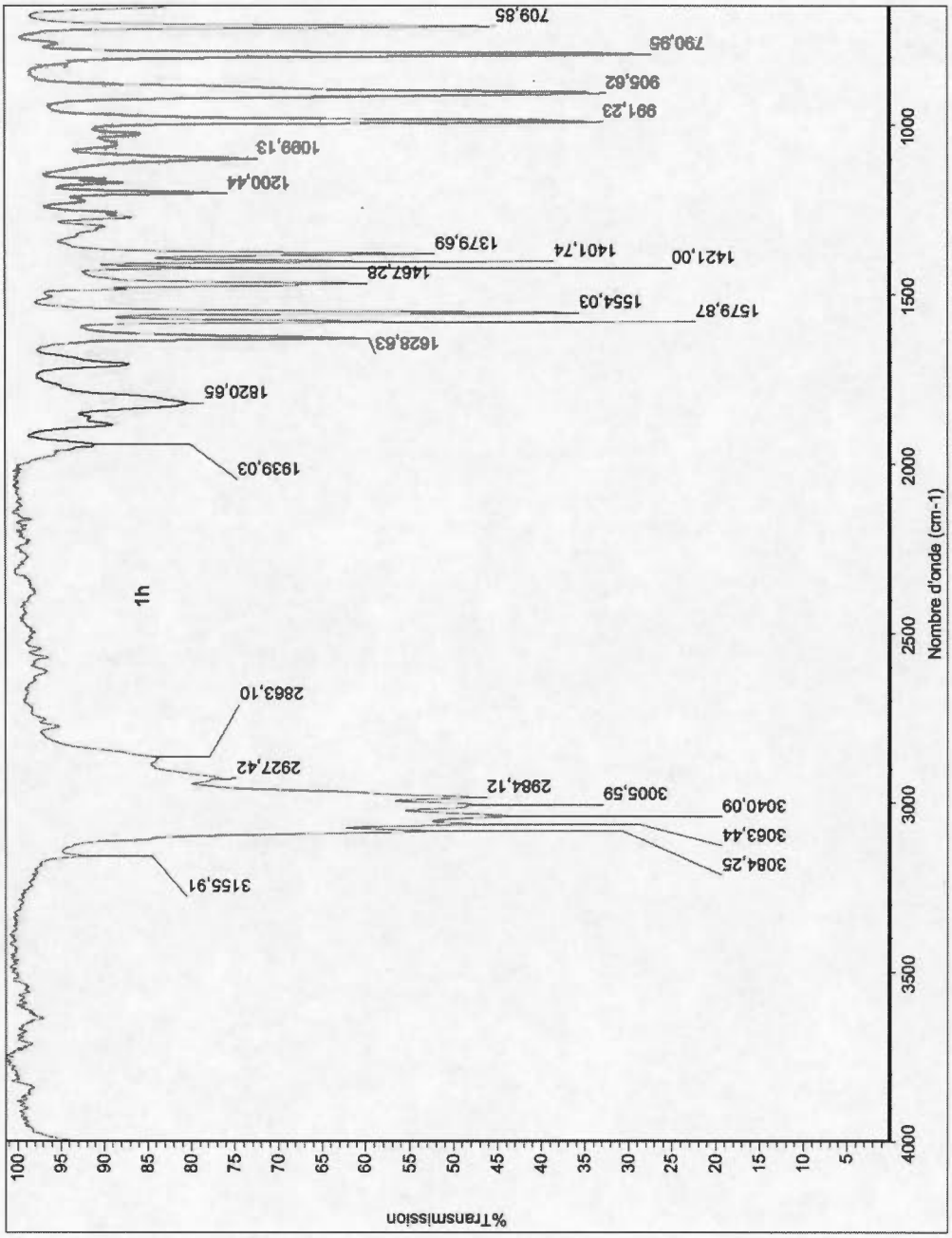
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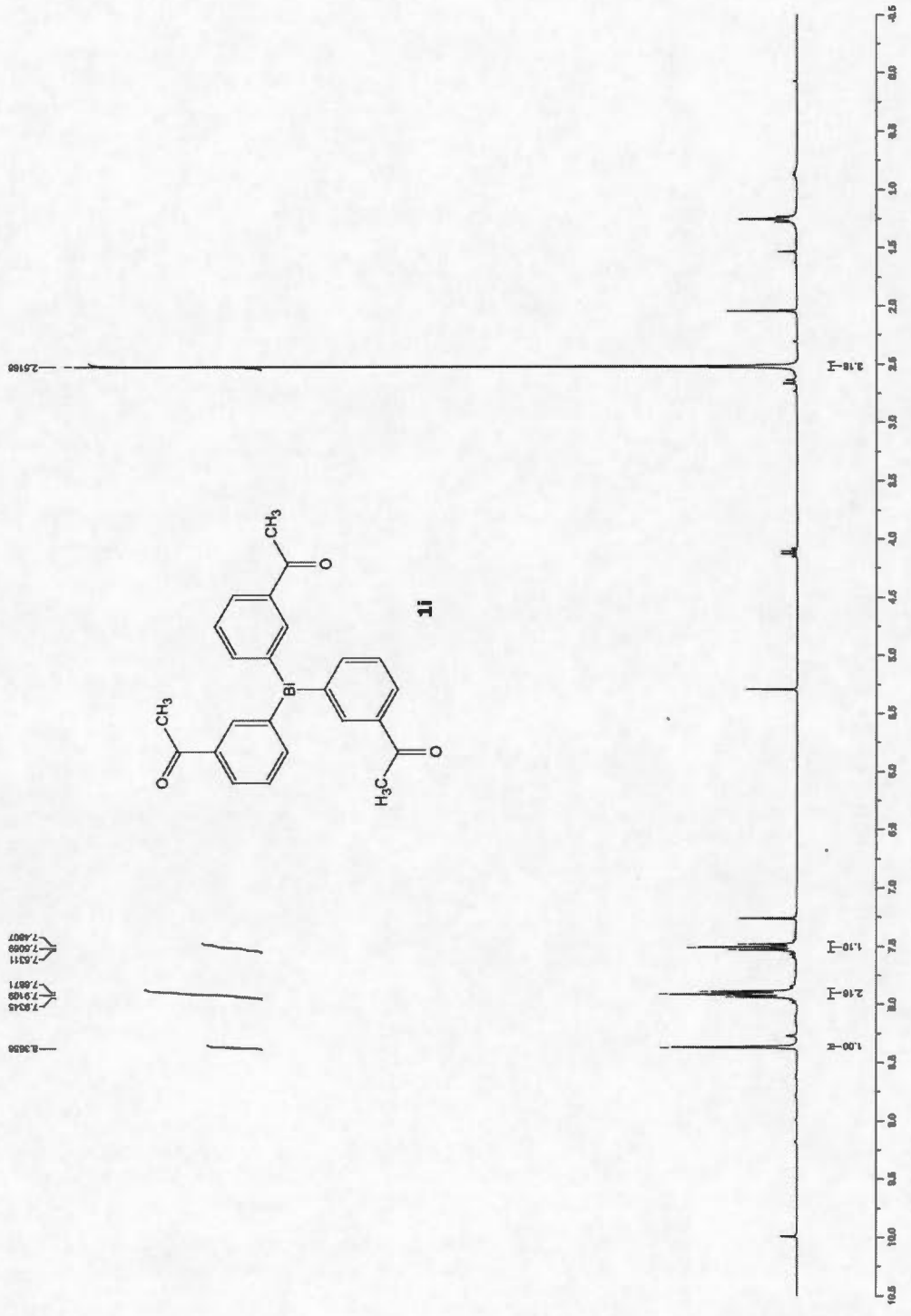
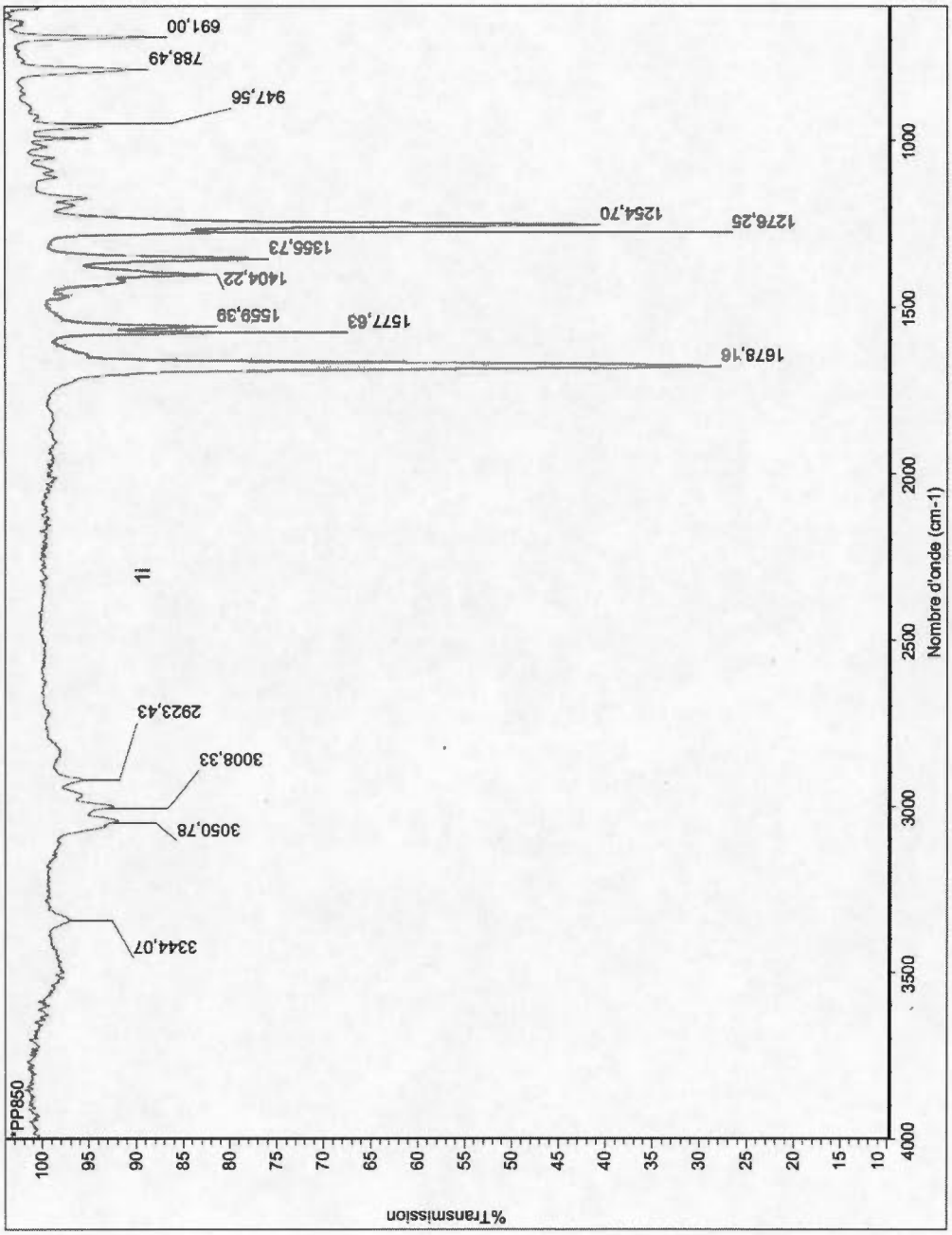
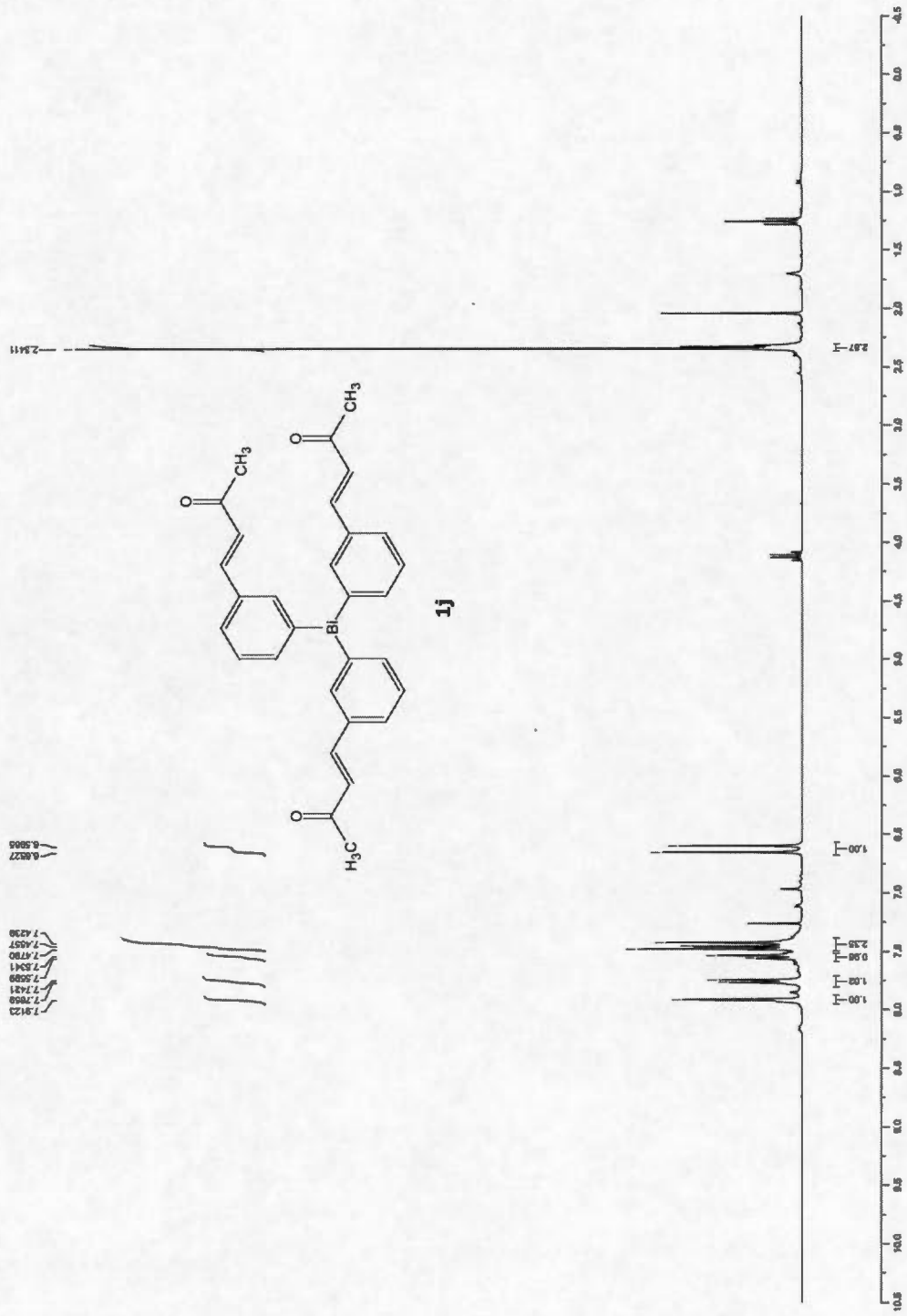
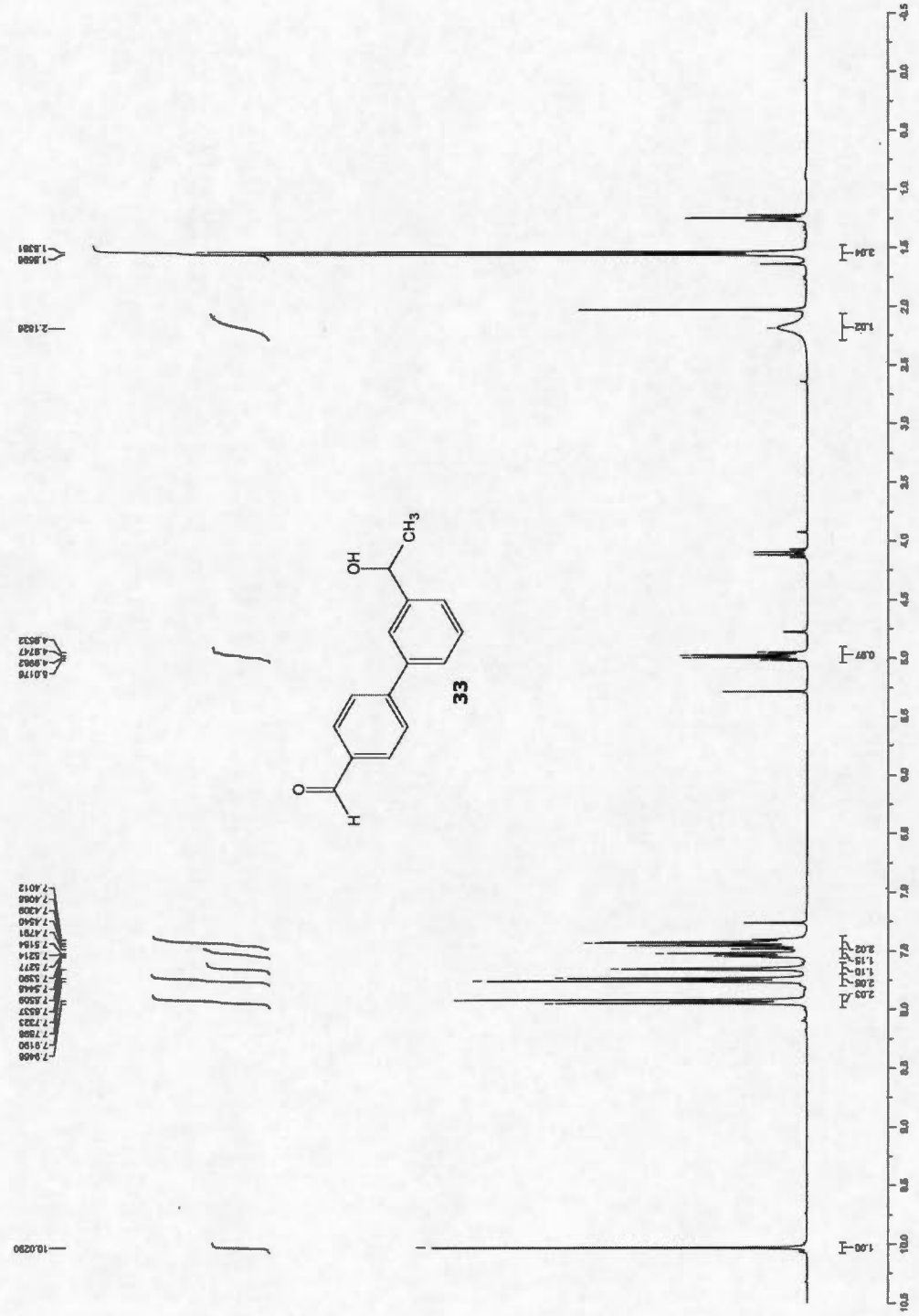
Nombre d'onde (cm-1)
1h
3155,91
3084,25
3063,44
3040,09
3005,59
2984,12
2927,42
2863,10
1939,03
1820,65
1628,63
1579,87
1554,03
1467,28
1421,00
1401,74
1379,69
1200,44
1089,13
991,23
905,62
790,95
709,85

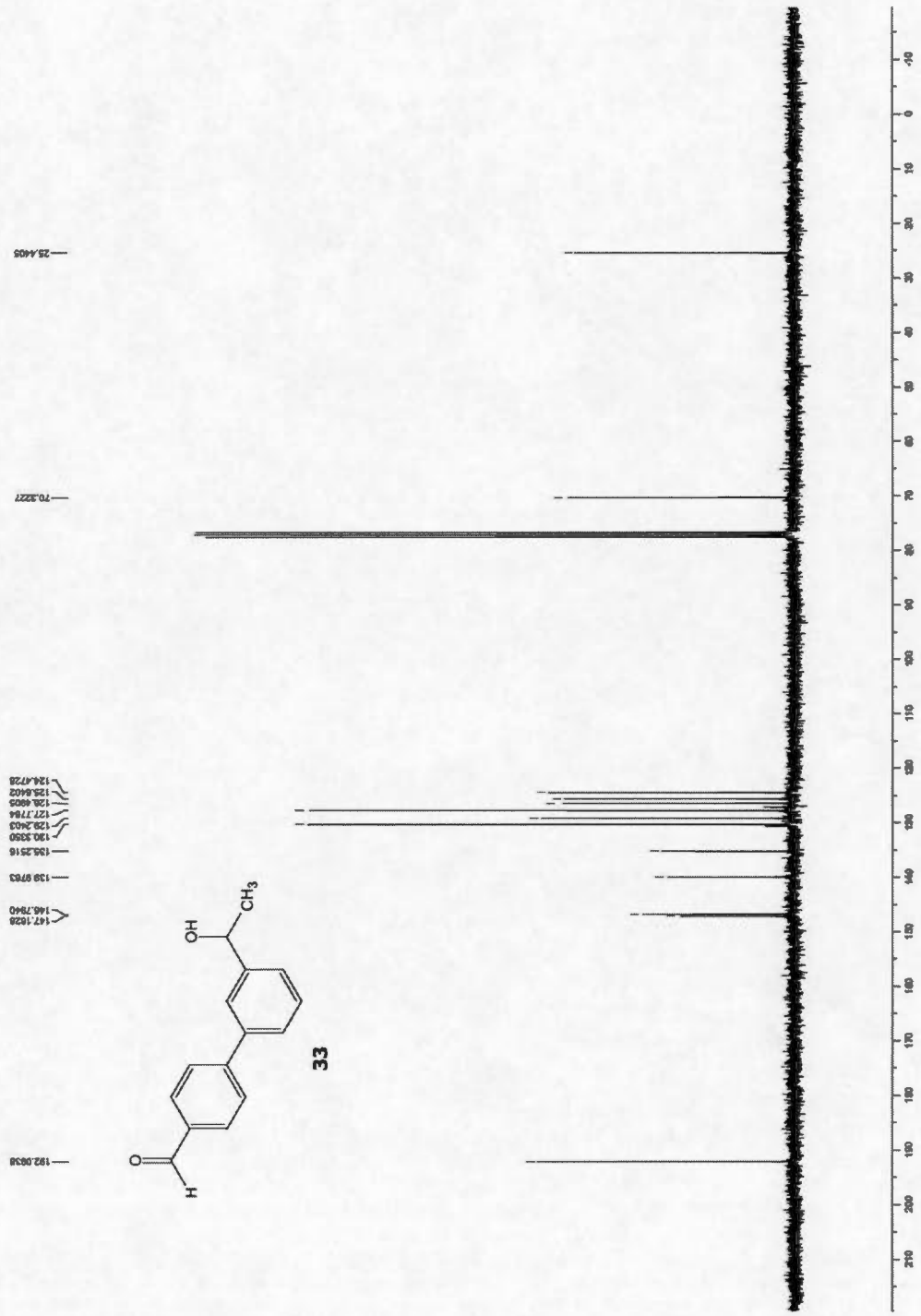

2.5168
8.3638
7.8343
7.9109
7.8871
7.4311
7.4088
7.4807
3.18
1.10
2.16
1.00
1i
CH3
O
Bi
H3C

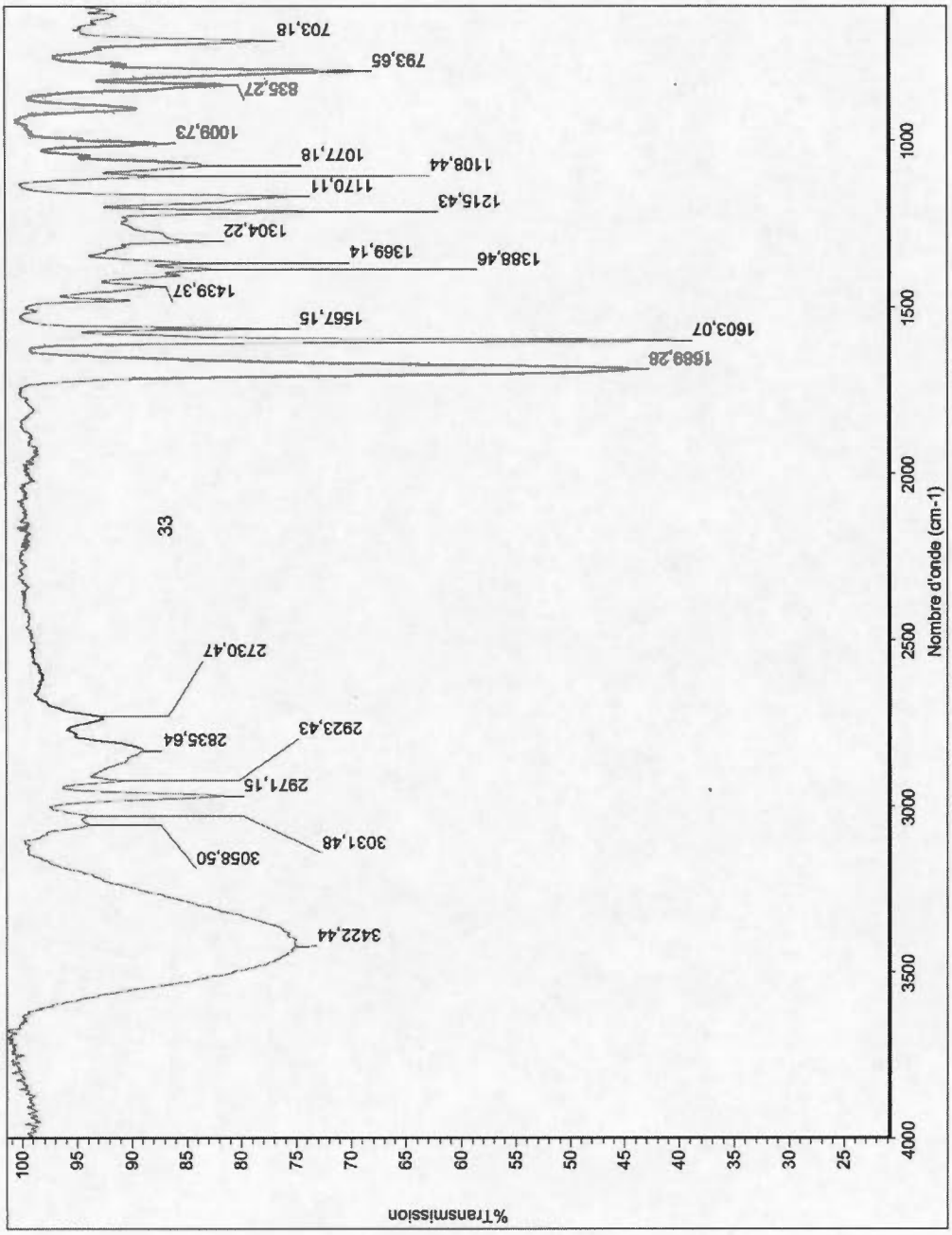

1i
Bi
CH3
O
H3C
142.1785
138.7586
137.8768
131.1131
131.0576
128.3453
188.4004
26.7463

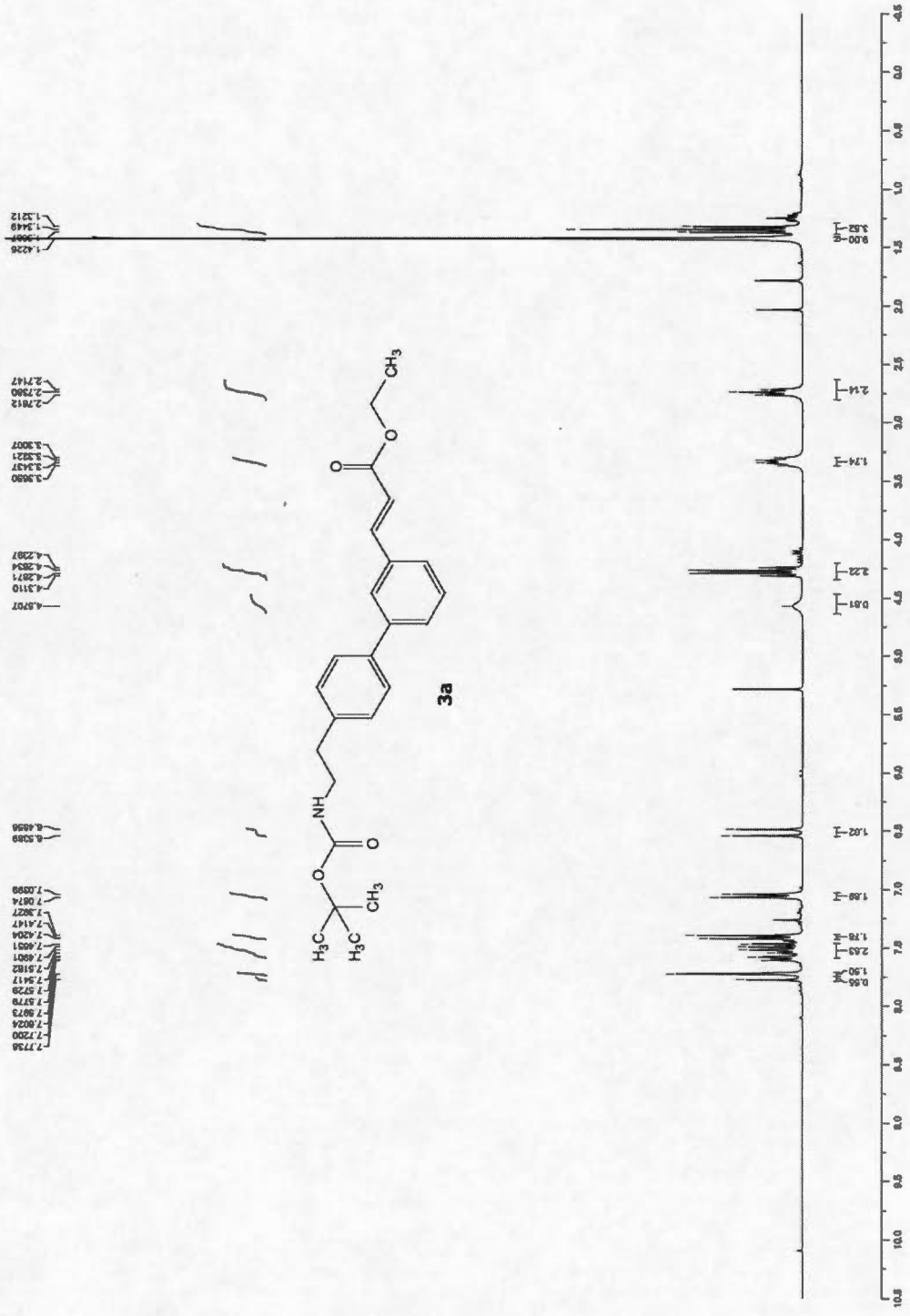

*PP850
%Transmission
Nombre d'onde (cm-1)
3344,07
3050,78
3008,33
2923,43
1678,16
1577,63
1558,38
1404,22
1355,73
1276,25
1254,70
947,56
788,49
691,00

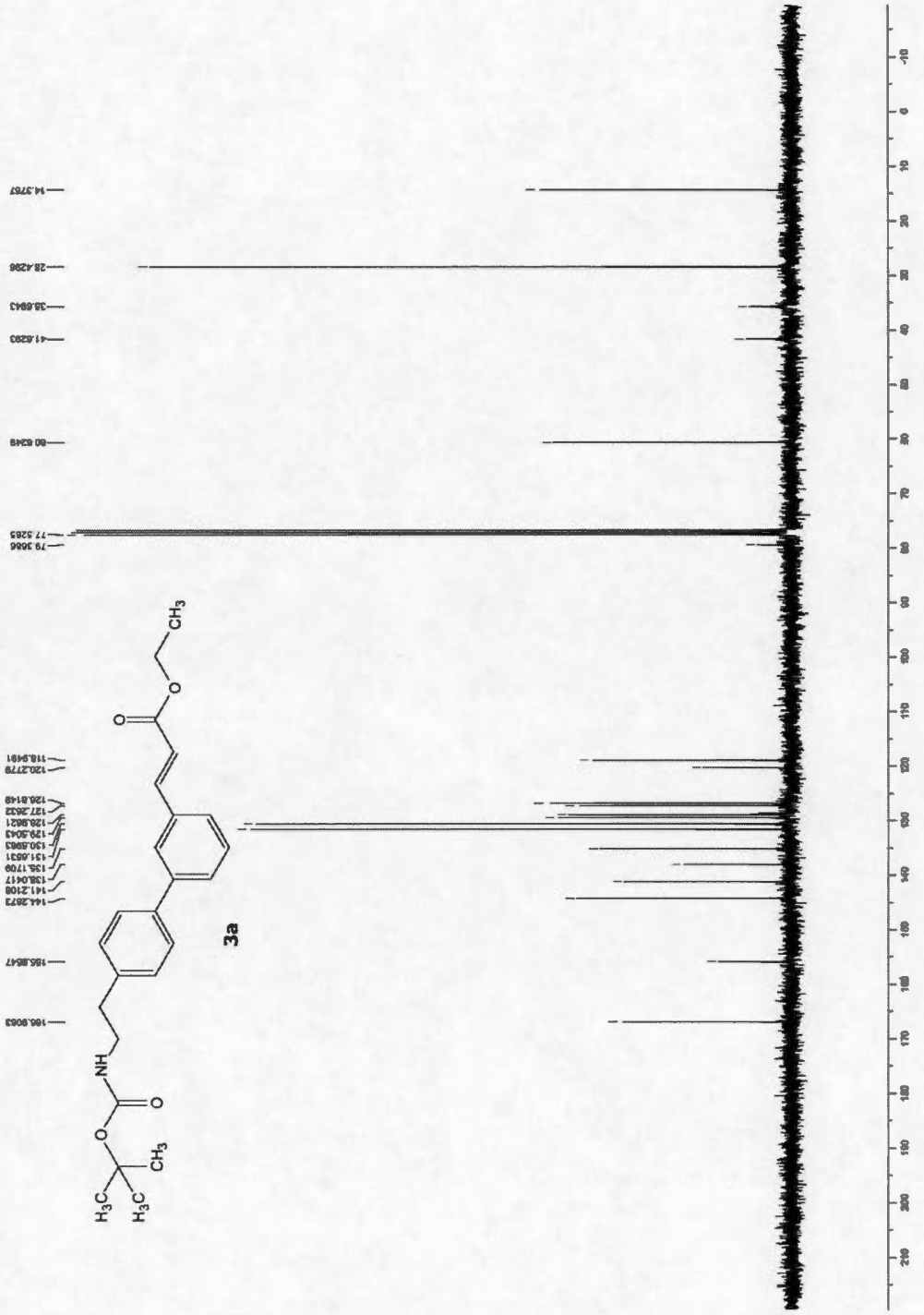

1j
Bi
O
CH3
H3C
2.3411
2.87
1.00
2.35
0.96
1.02
1.00
8.5865
8.4827
7.9123
7.7959
7.7421
7.5539
7.5341
7.4780
7.4657
7.4239

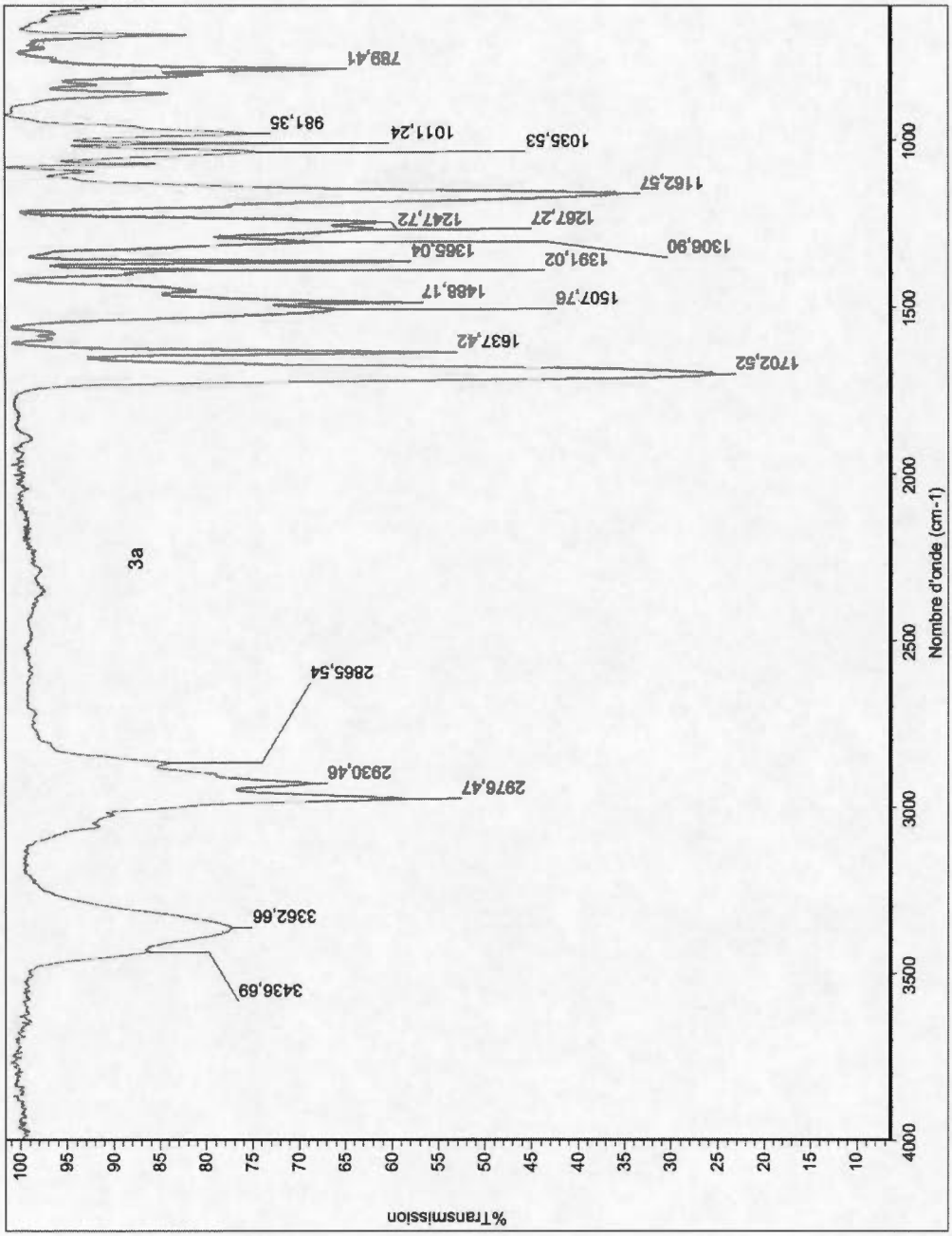

OH
CH3
O
H
33

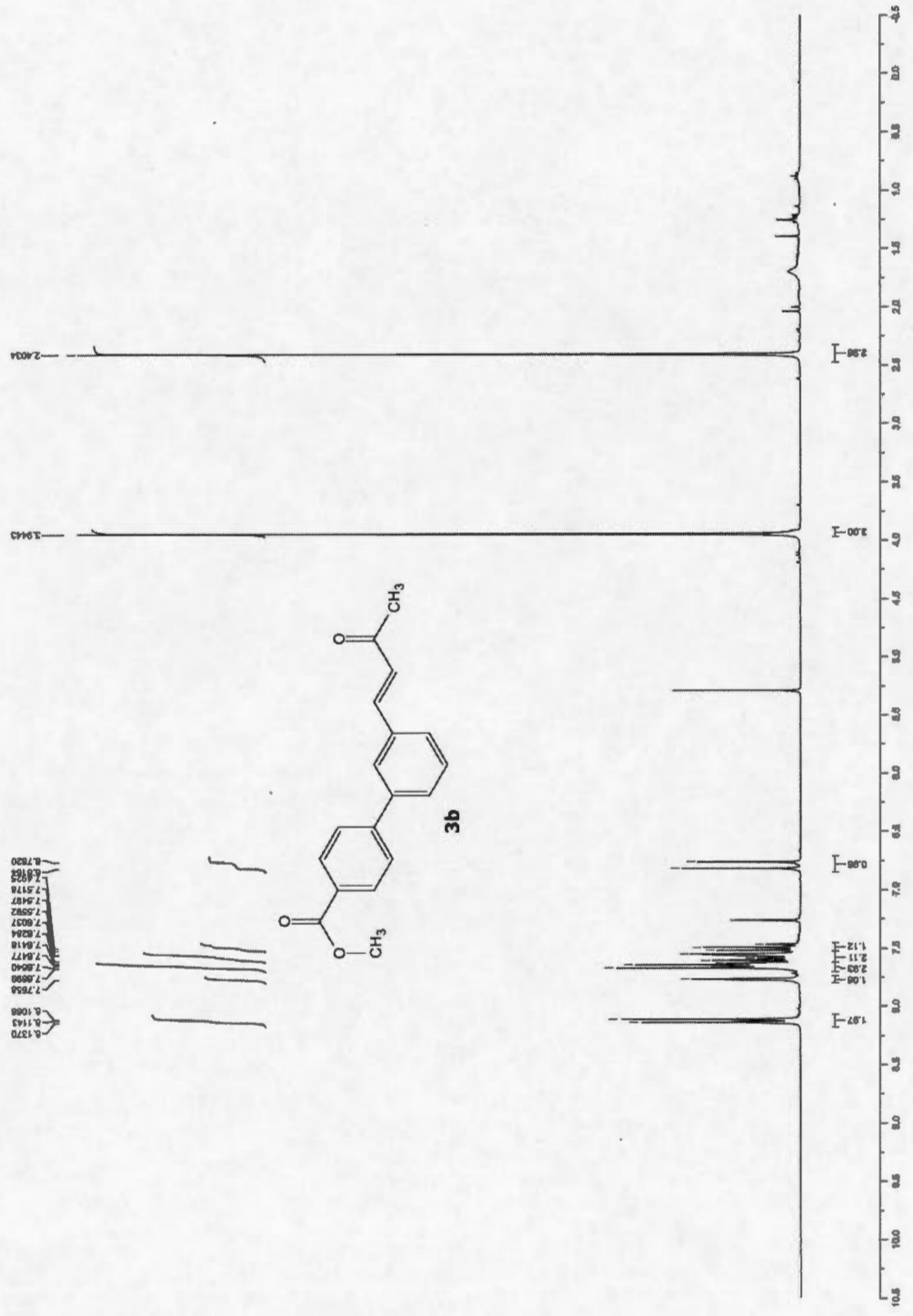

192.0838
147.1628
146.7840
139.8763
136.2516
130.3350
129.2403
127.7784
126.4805
125.6402
124.4728
70.3227
25.4405
OH
CH3
O
H
33

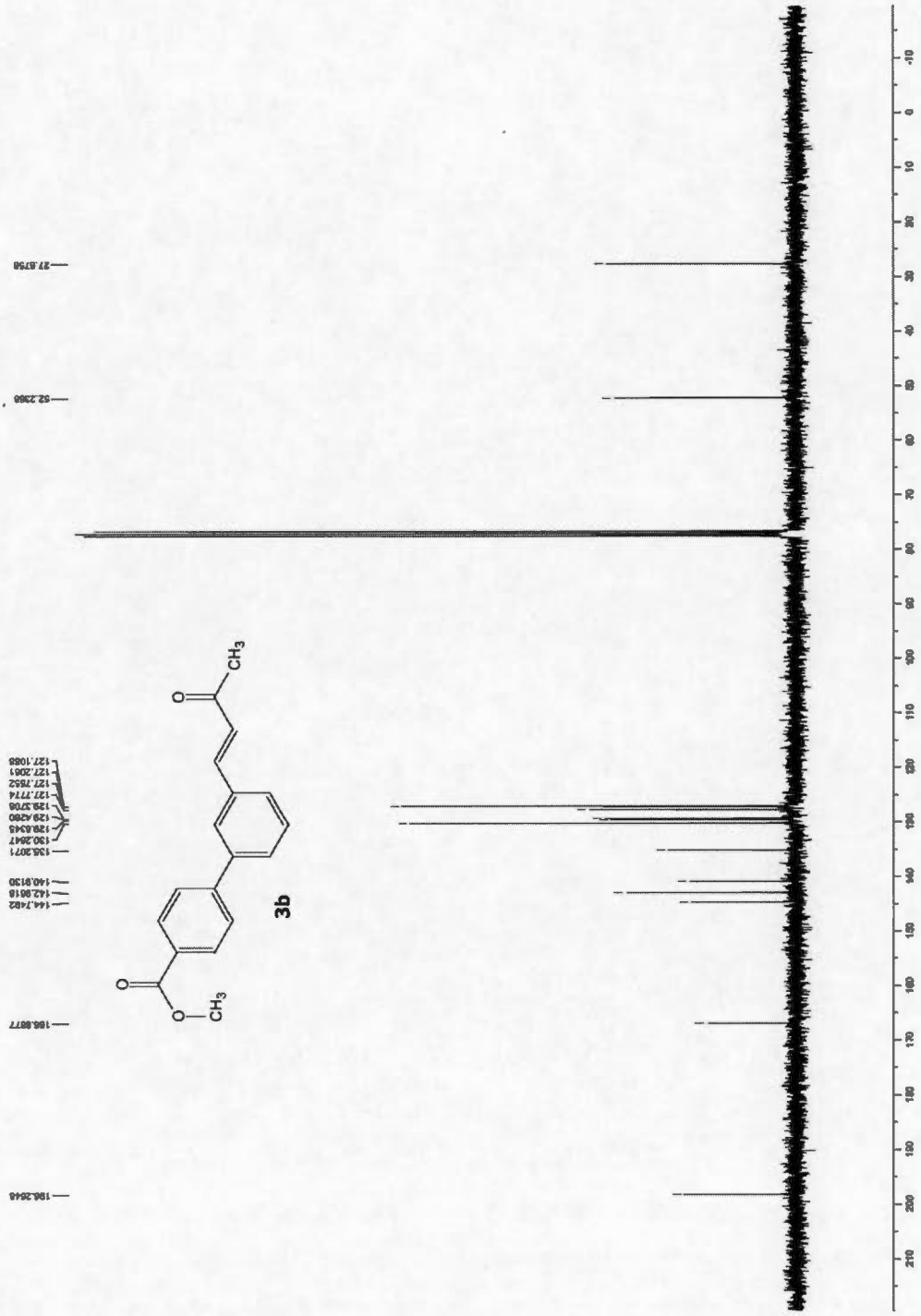

%Transmission
Nombre d'onde (cm-1)
4000
3500
3000
2500
2000
1500
1000
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
3422,44
3058,50
3031,48
2971,15
2923,43
2835,64
2730,47
1689,28
1603,07
1567,15
1439,37
1388,46
1369,14
1304,22
1215,43
1170,11
1108,44
1077,18
1009,73
835,27
793,65
703,18
33

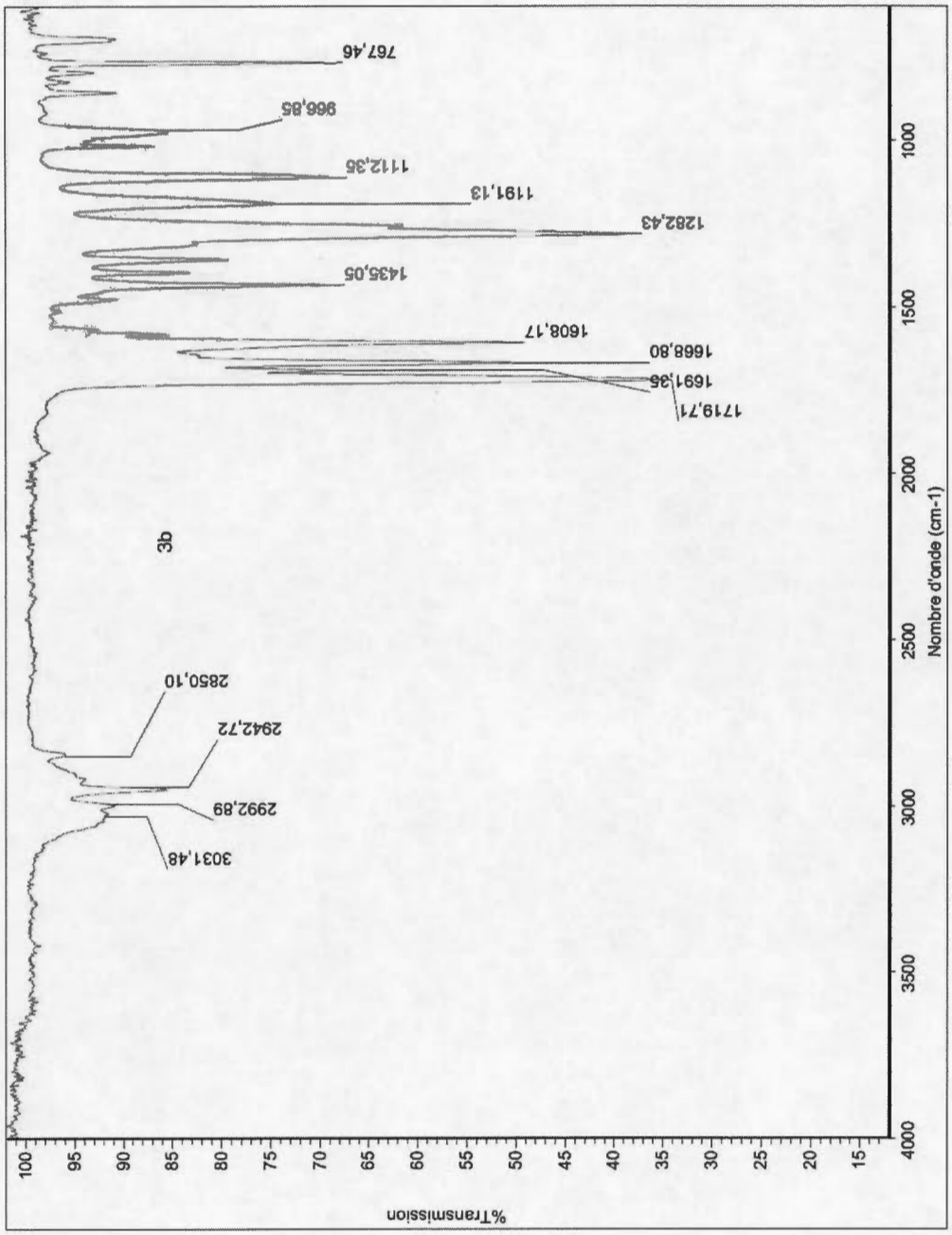

3a

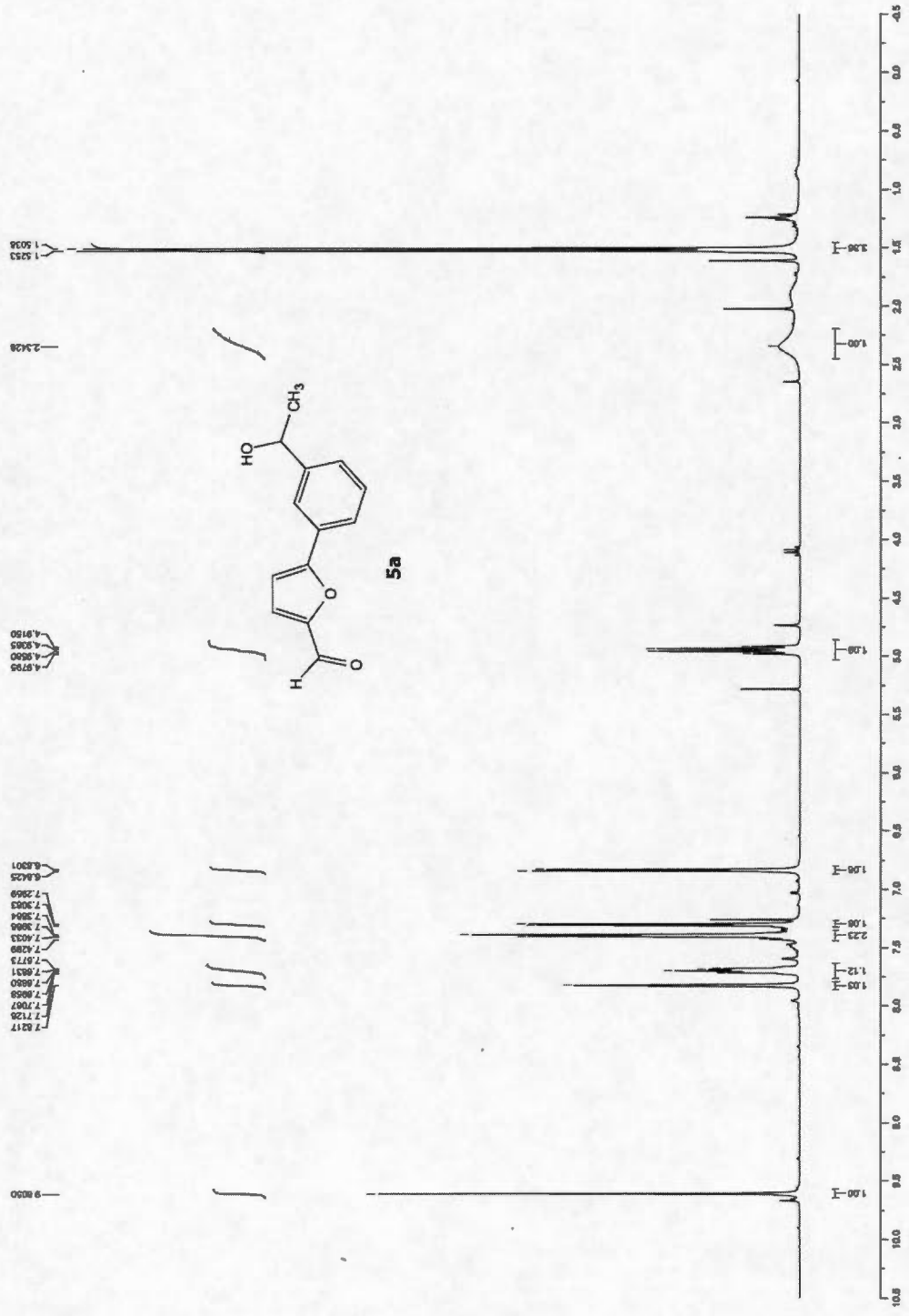

14.3767
28.4286
38.6843
41.6283
60.6348
77.5285
79.3666
118.9481
120.2779
126.8148
127.3632
128.9021
129.3043
130.5863
131.6531
135.1709
138.0417
141.2108
144.3673
166.8547
166.9063
3a

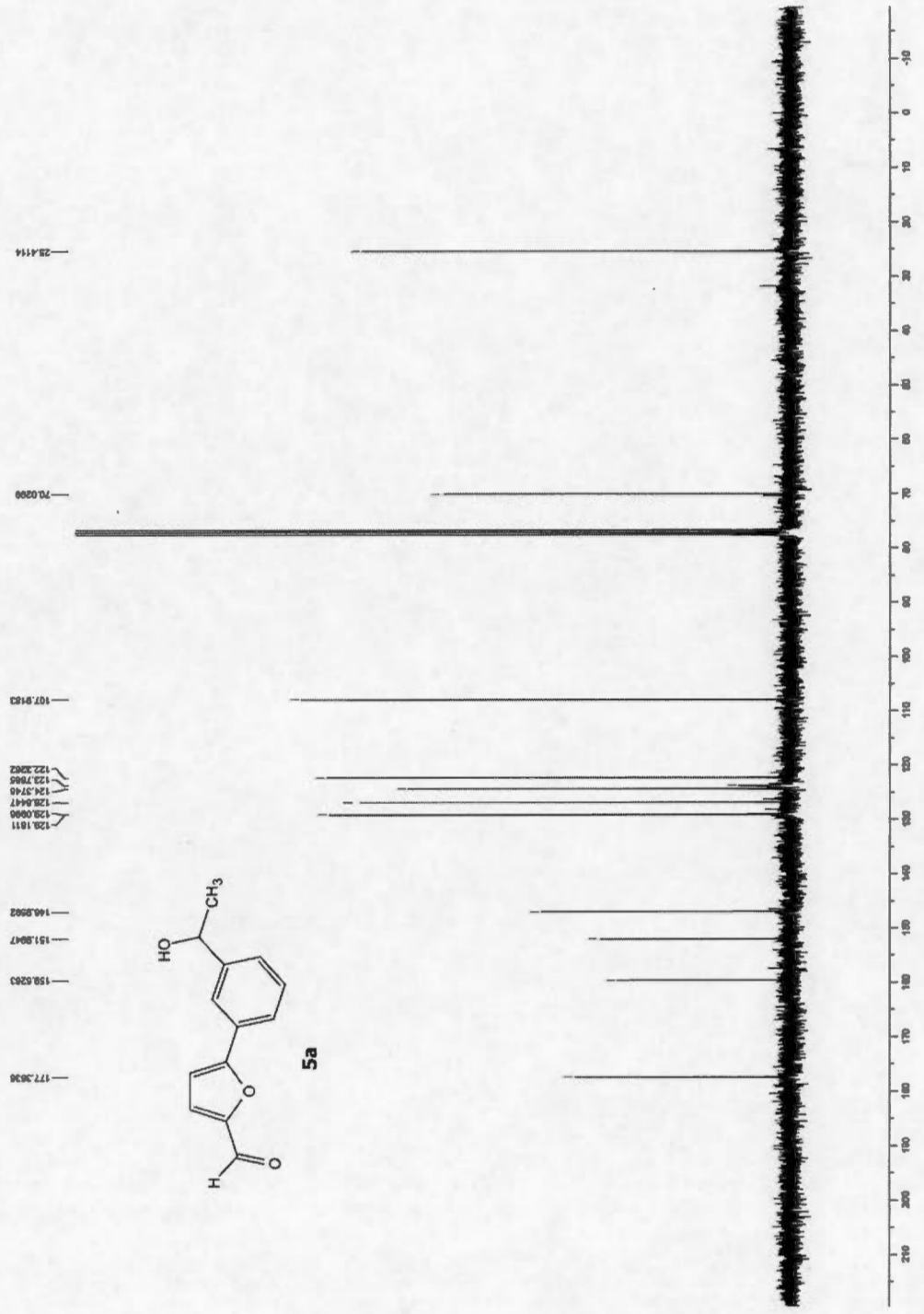

%Transmission
Nombre d'onde (cm-1)
3a
3436,89
3362,66
2976,47
2930,46
2865,54
1702,52
1637,42
1507,76
1488,17
1391,02
1365,04
1306,90
1267,27
1247,72
1162,57
1035,53
1011,24
981,35
788,41

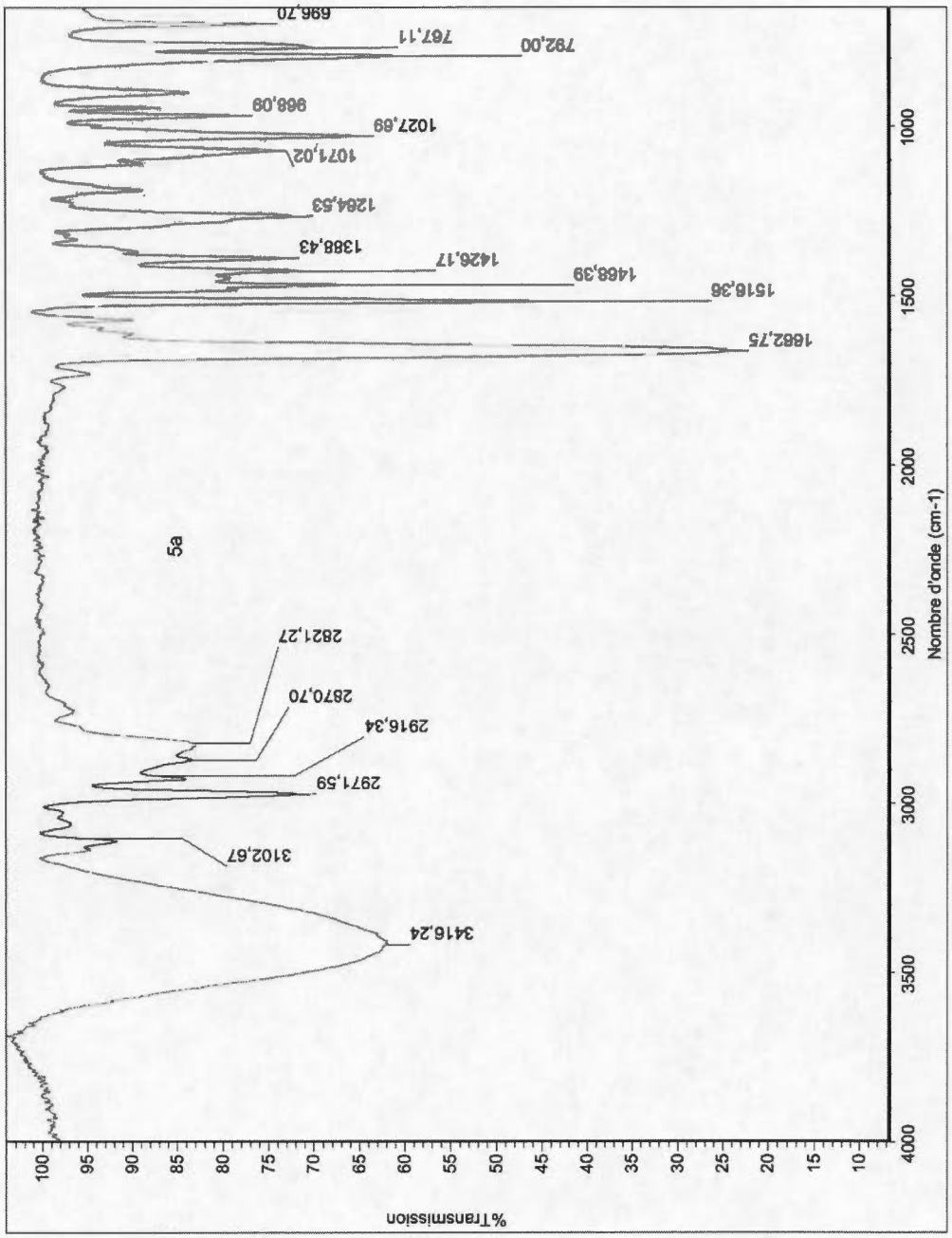

3b
CH3
CH3
O
O
O
2.4034
3.9443
8.1370
8.1143
8.1068
7.7820
7.7636
7.7590
7.7440
7.7418
7.7377
7.6264
7.6037
7.5982
7.5787
7.5178
7.4925
7.4768
8.7820
2.36
3.00
0.98
1.97
1.12
2.11
2.03
1.08

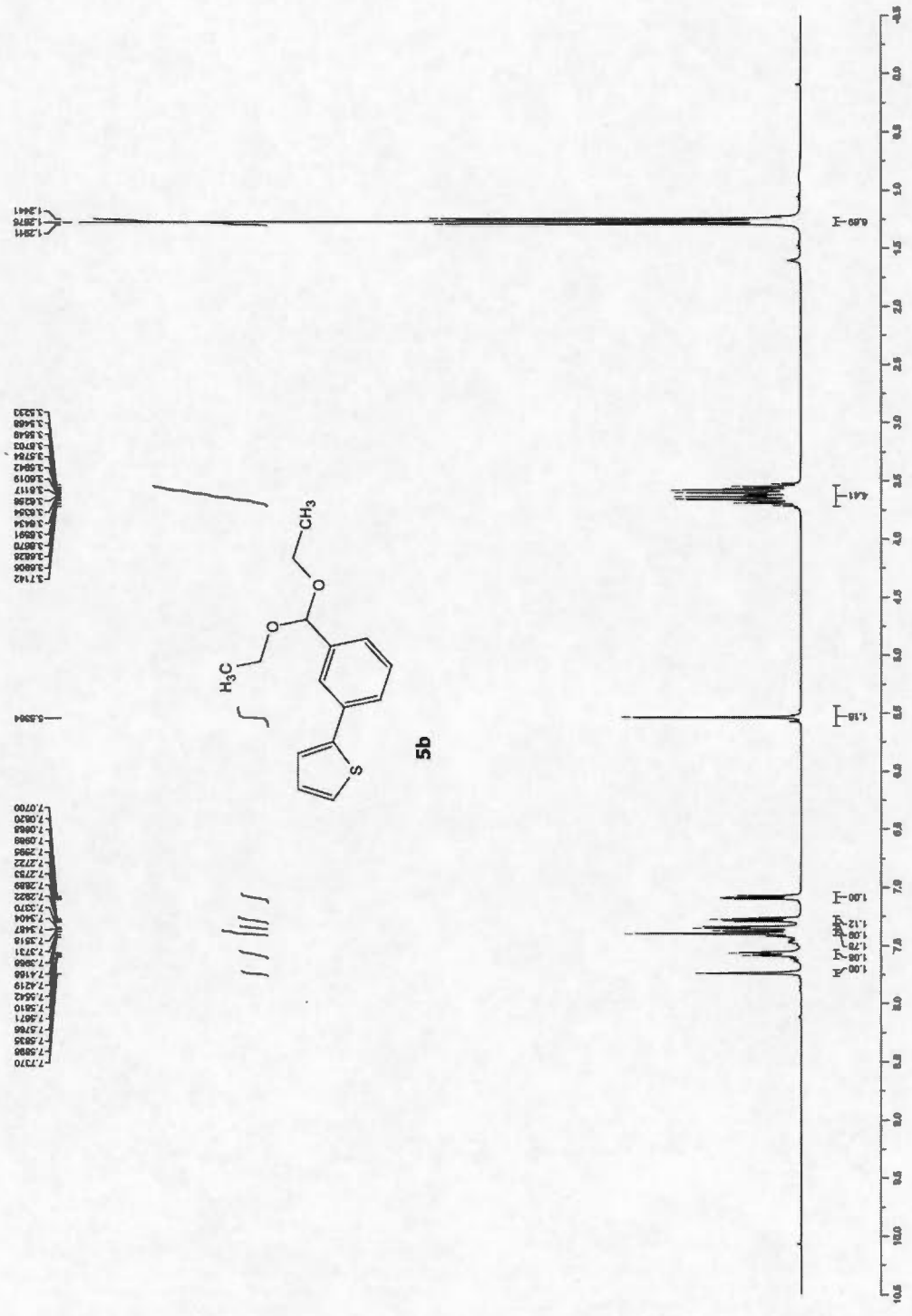

27.8758
52.2366
127.1088
127.2061
127.7552
127.7774
129.3706
129.4280
129.8343
130.2647
135.3071
140.8130
142.8616
144.7482
166.8877
198.2646
3b

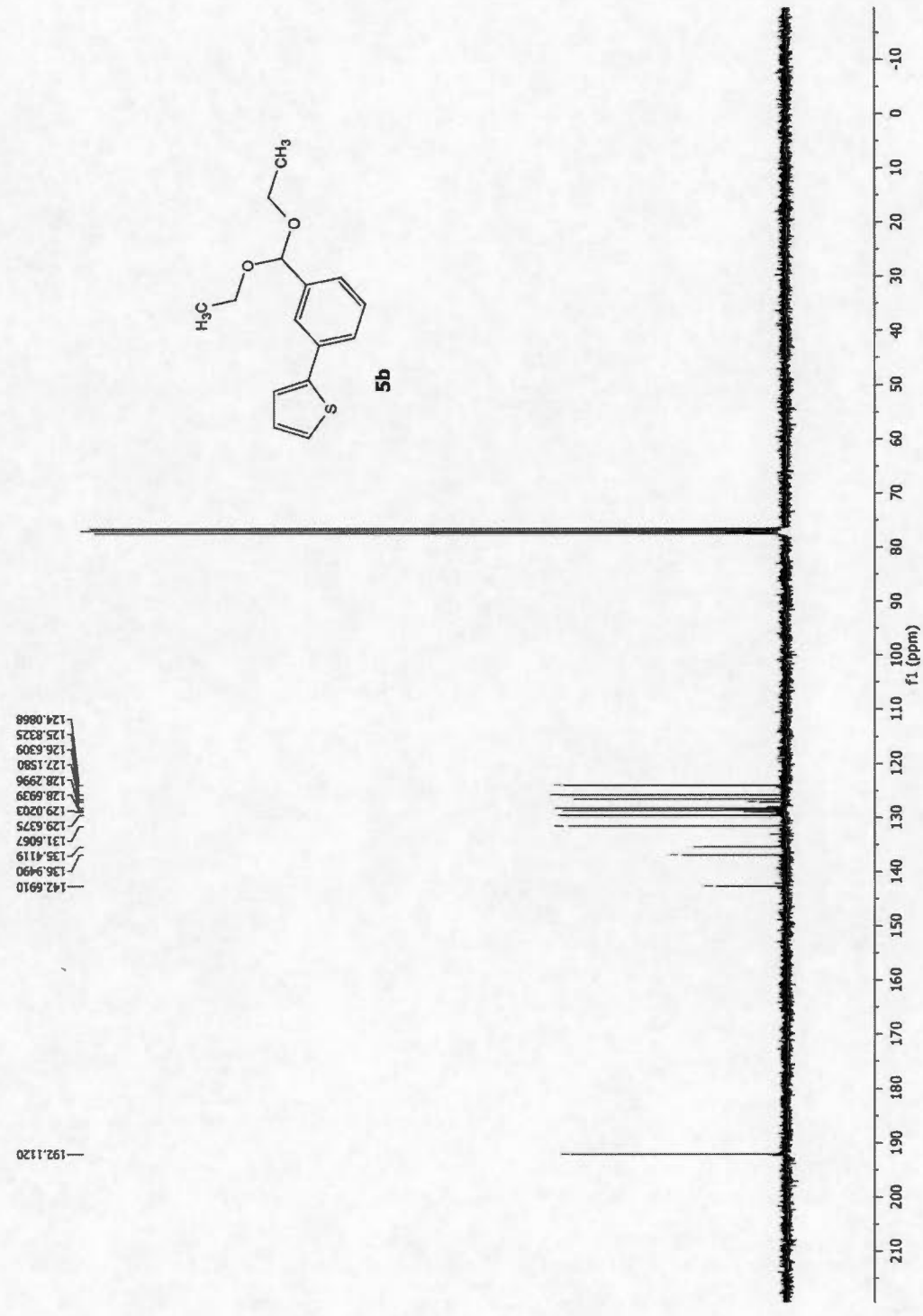

%Transmission
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
4000
3500
3000
2500
2000
1500
1000
Nombre d'onde (cm-1)
3b
3031,48
2992,89
2942,72
2850,10
1719,71
1691,35
1668,80
1608,17
1435,05
1282,43
1191,13
1112,35
966,85
767,46

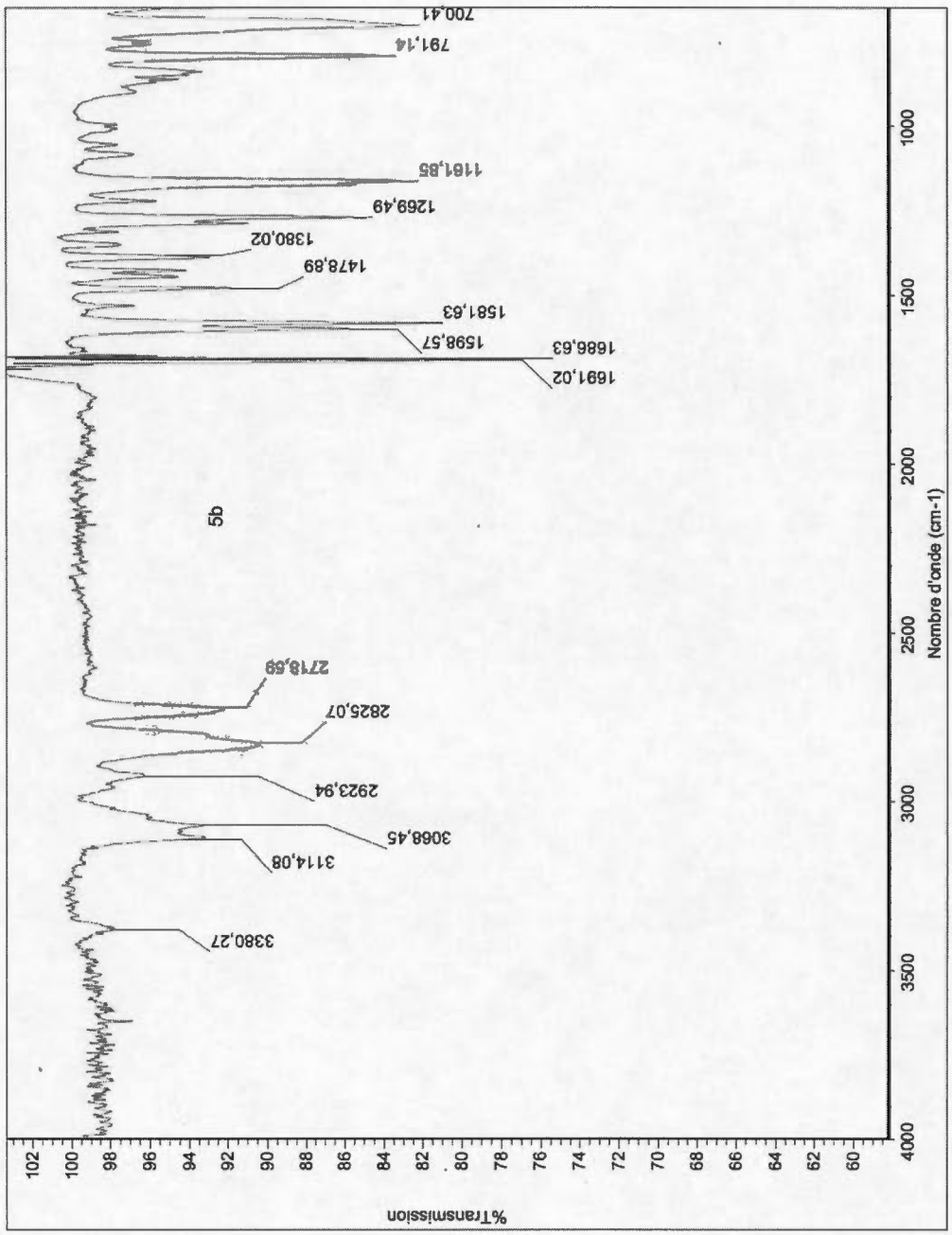

HO
CH3
O
H
O
5a

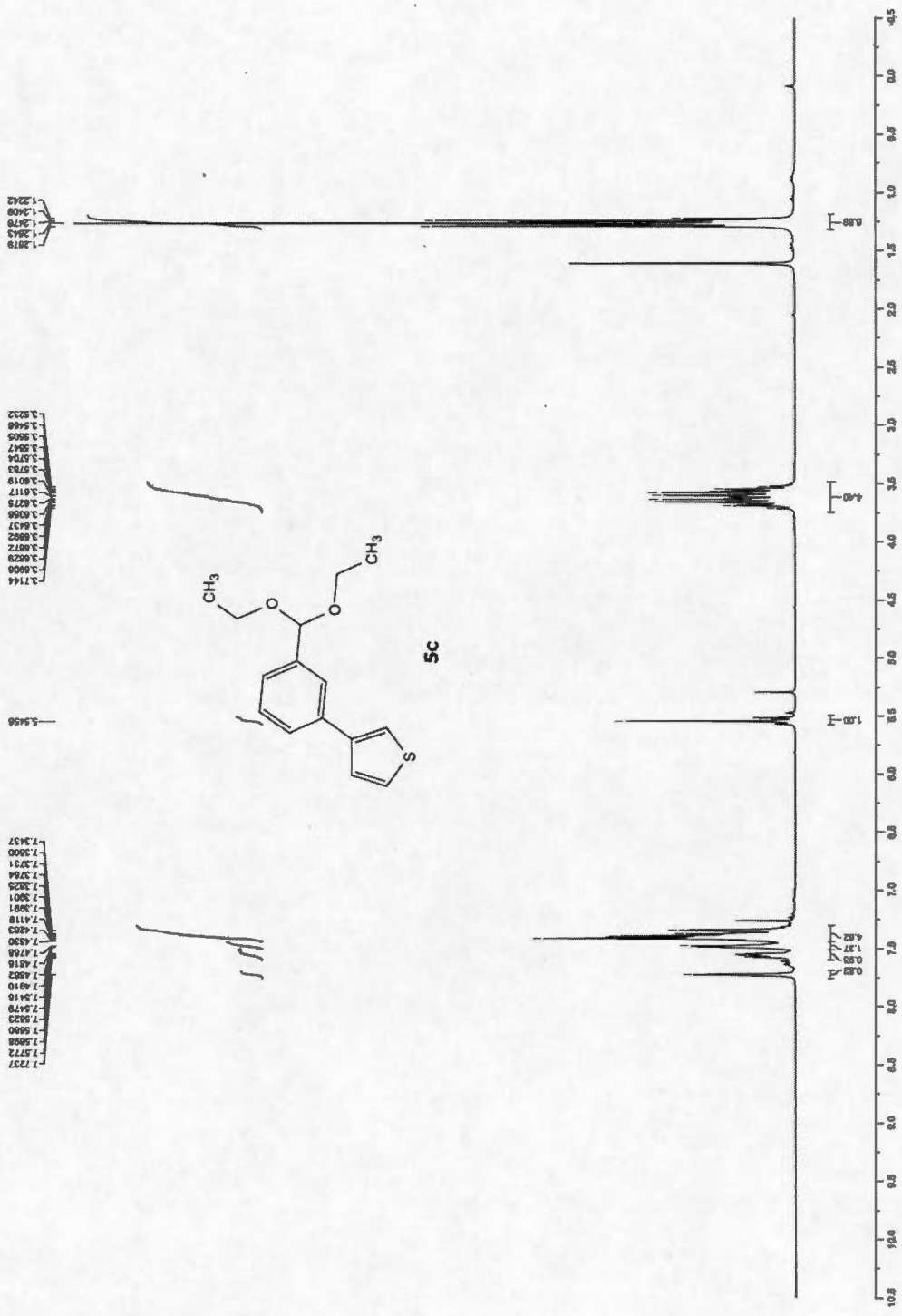

177.3636
158.6263
151.8047
146.8562
129.1811
129.0996
128.9447
124.3746
123.7986
122.3262
107.9163
70.0299
23.4114
HO
CH3
O
H
O
5a

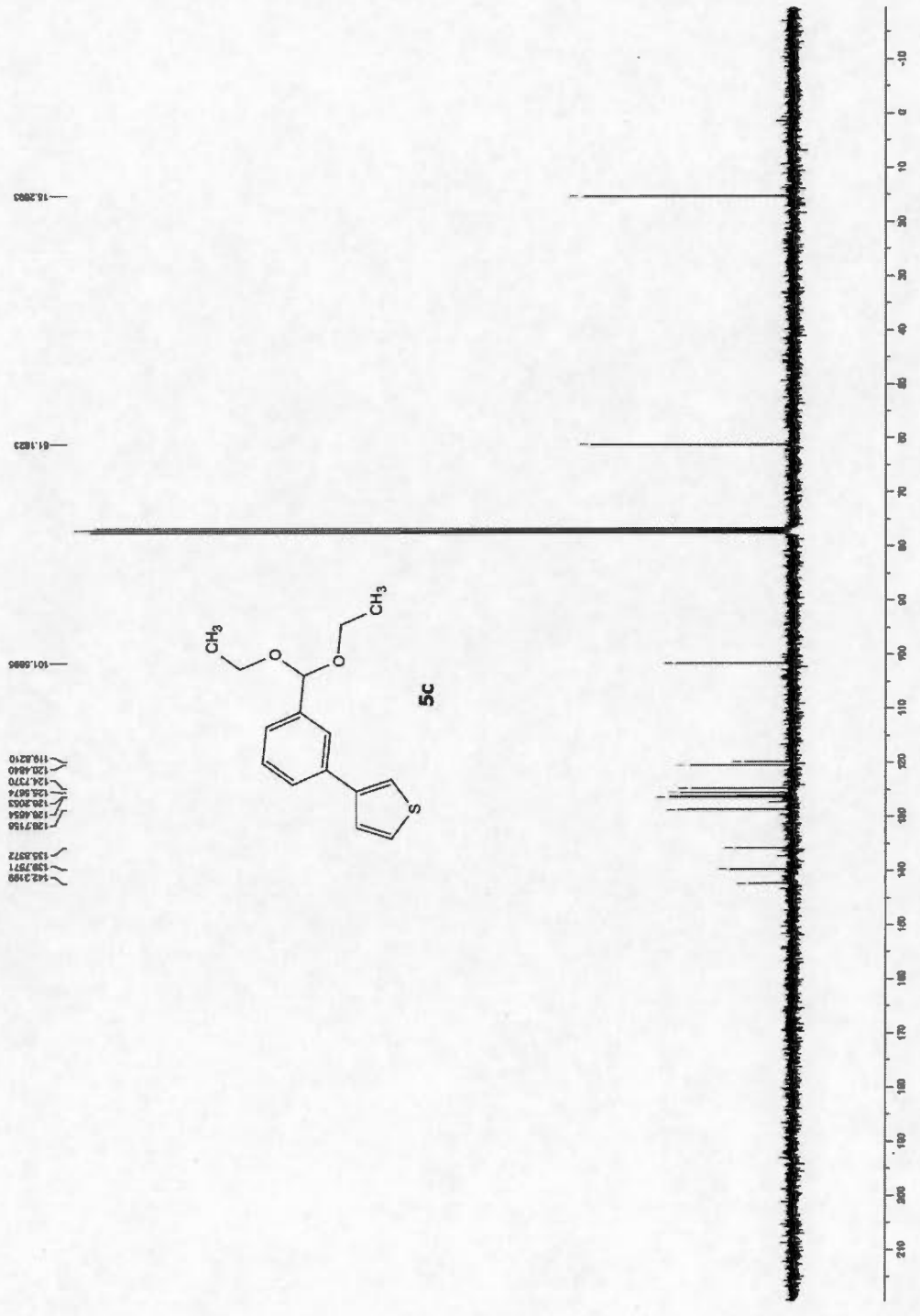

%Transmission
Nombre d'onde (cm-1)
5a
3416,24
3102,67
2971,59
2916,34
2870,70
2821,27
1682,75
1516,36
1468,39
1426,17
1388,43
1264,53
1071,02
1027,89
968,09
792,00
767,11
696,70

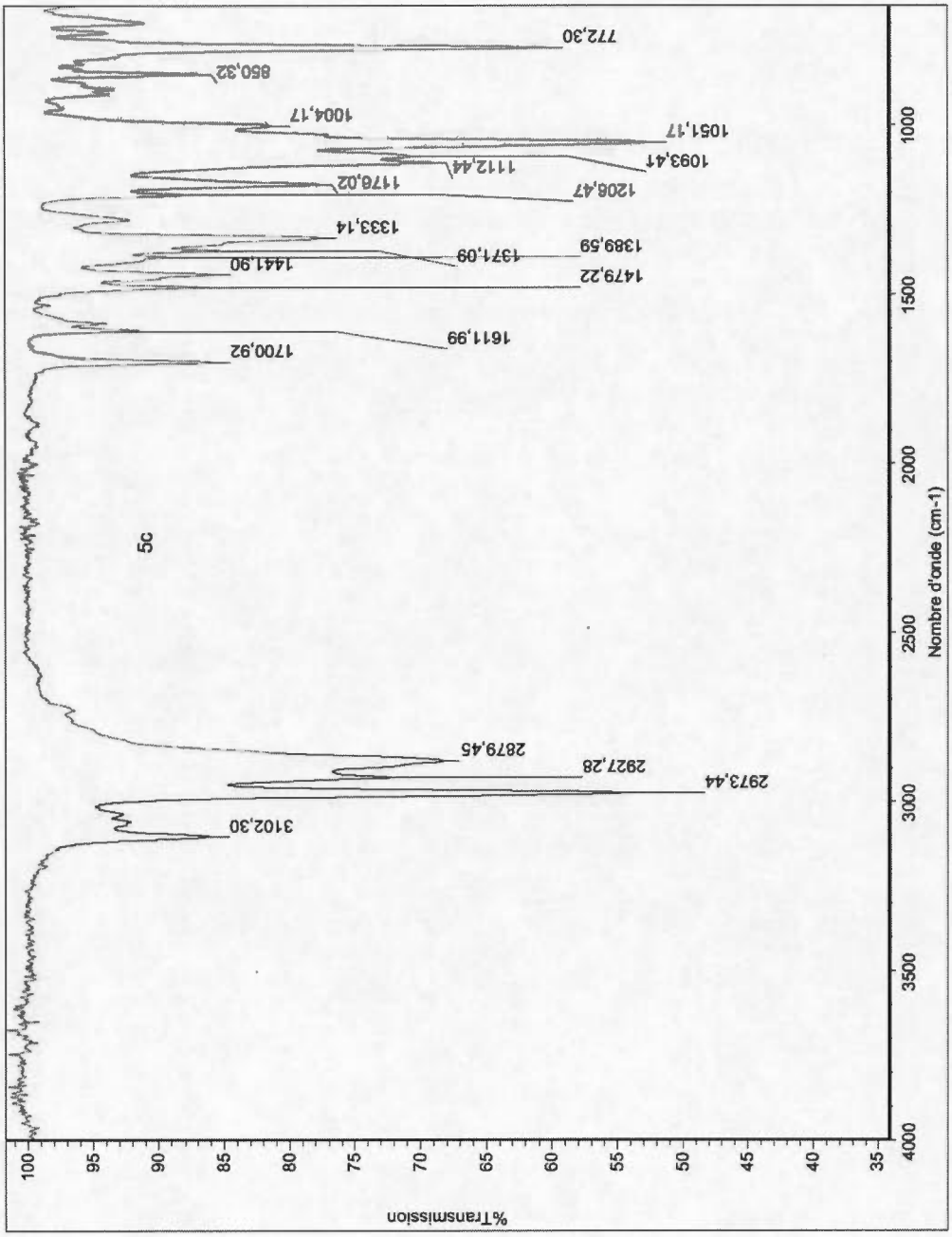

5b

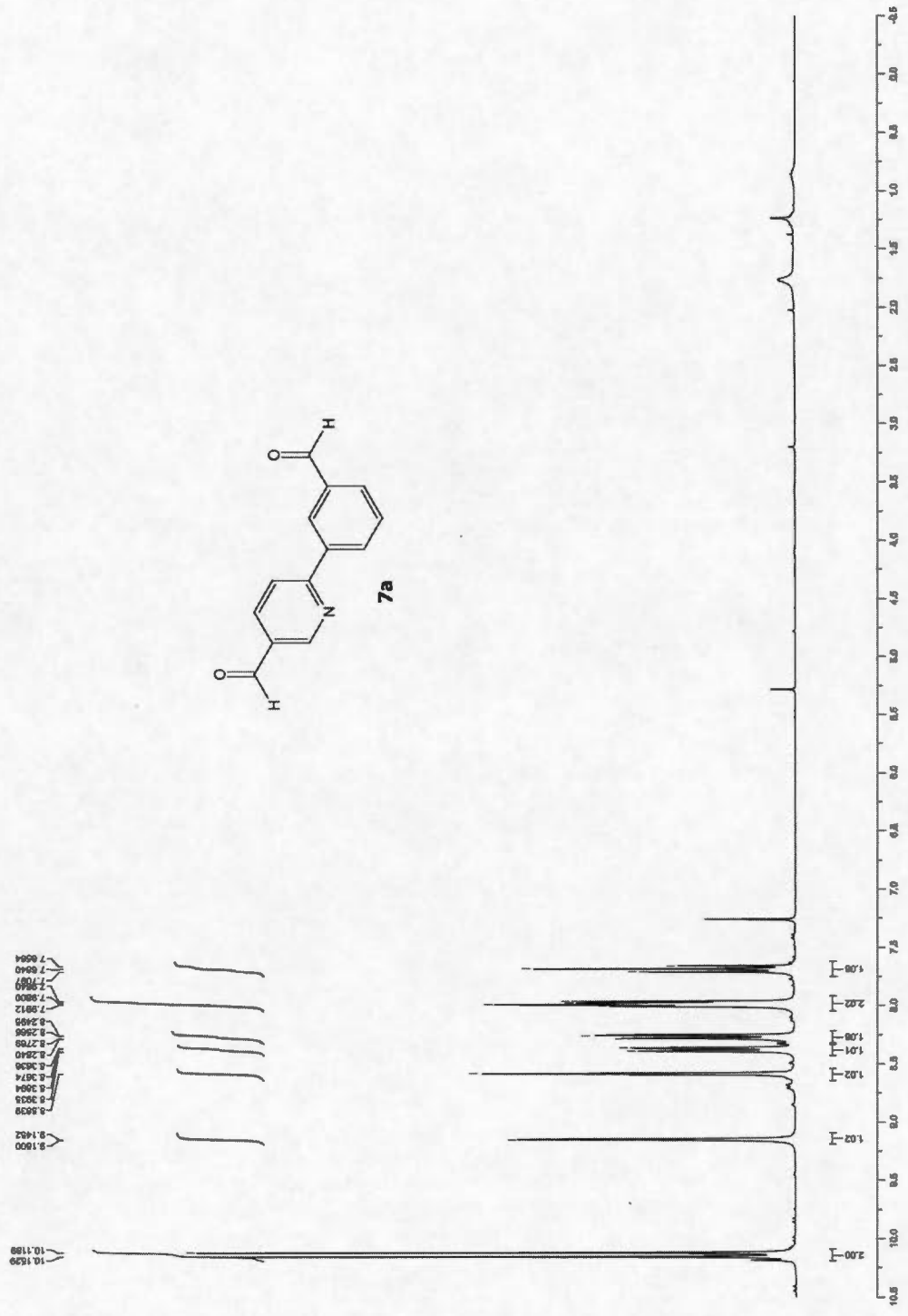

5b
192.1120
142.6910
136.9490
135.4119
131.6067
129.6375
129.0203
128.6939
128.2996
127.1580
126.6309
125.8325
124.0868
f1 (ppm)

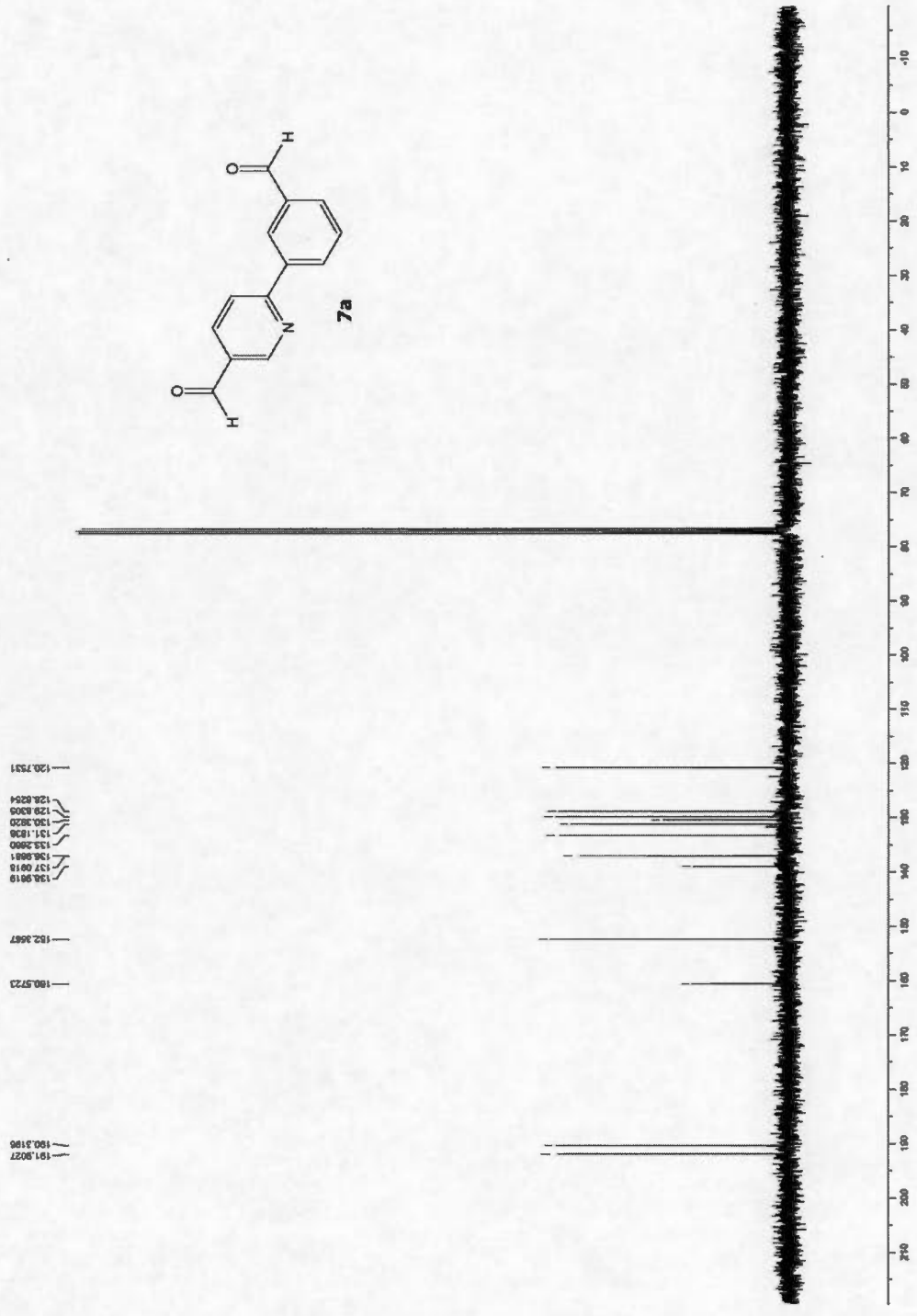

%Transmission
Nombre d'onde (cm-1)
5b
3380,27
3114,08
3068,45
2923,94
2825,07
2718,59
1691,02
1686,63
1598,57
1581,63
1478,89
1380,02
1269,49
1181,85
791,14
700,41

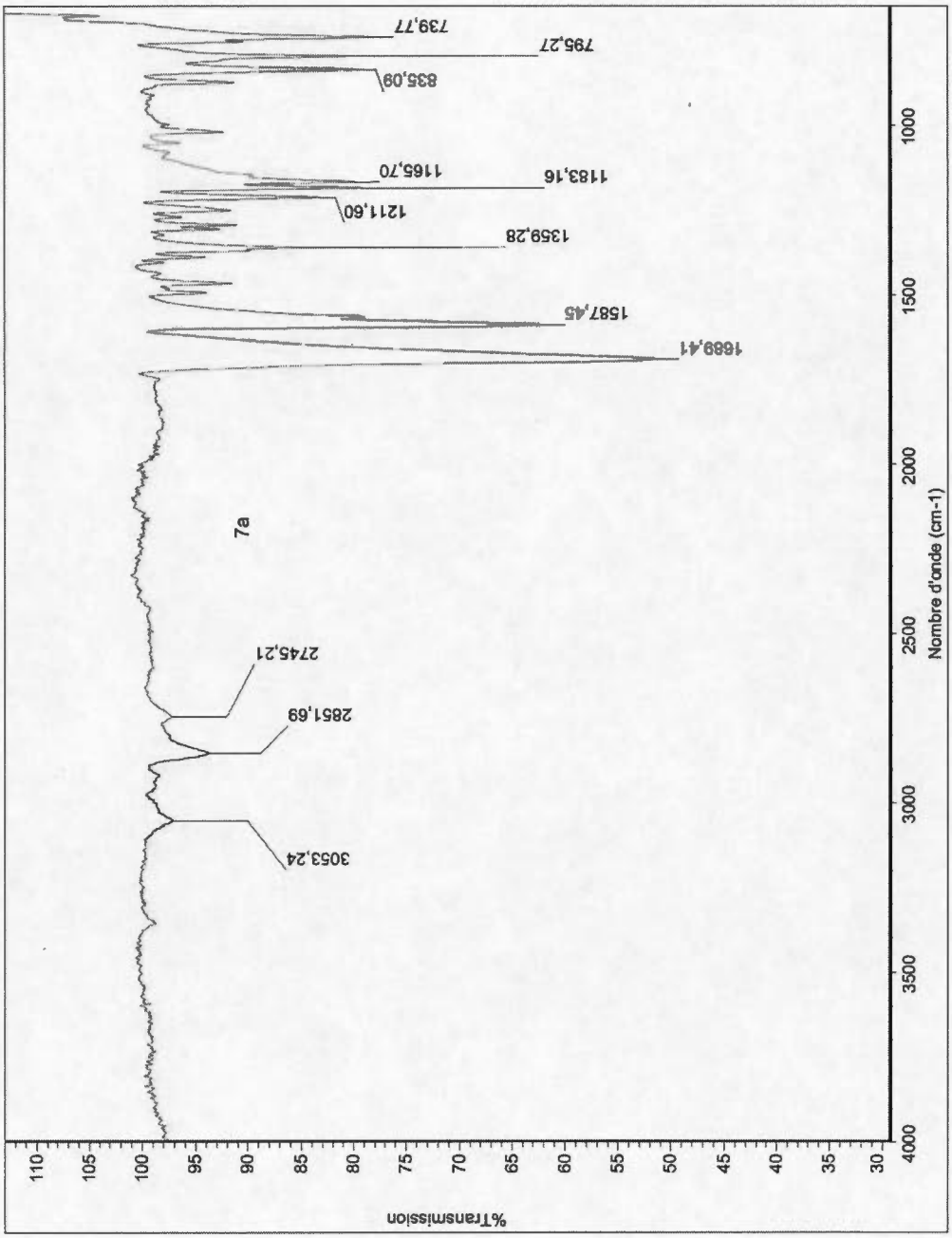

5c

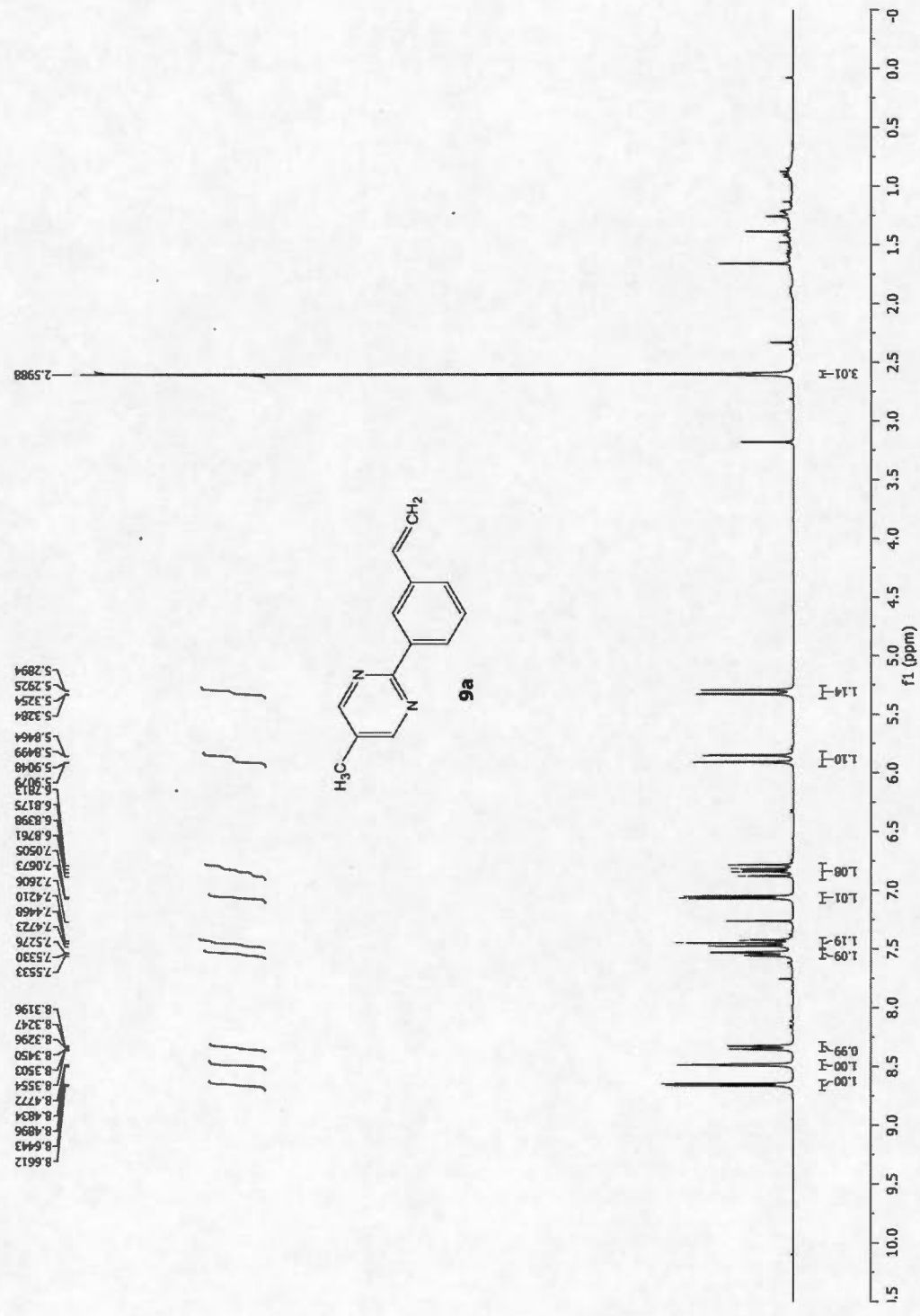

16.2865
61.1825
101.5885
110.8210
120.4840
124.7370
126.5674
128.3053
128.4654
128.7156
135.3572
138.7971
142.3189
5c

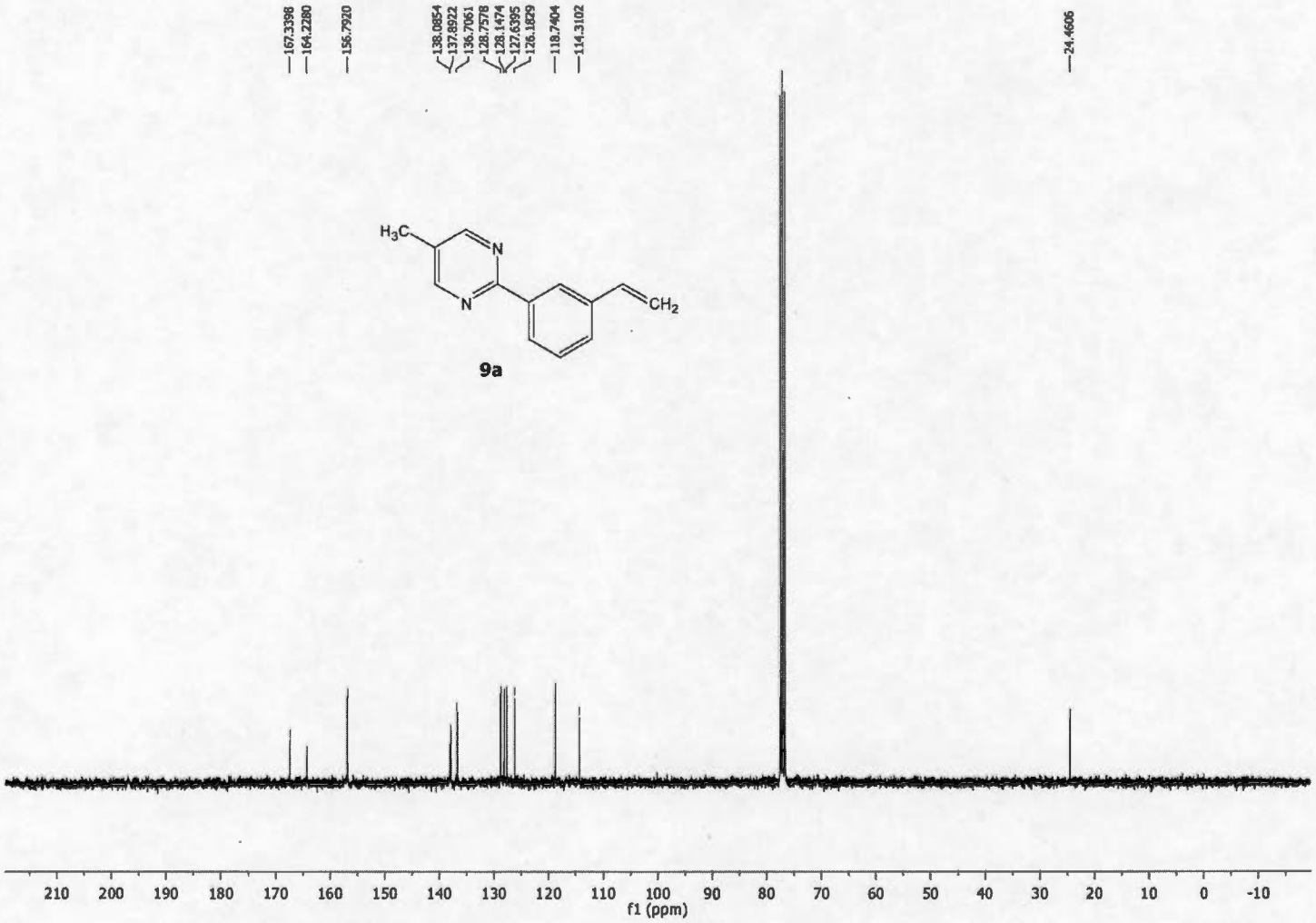

%Transmission
Nombre d'onde (cm-1)
5c
772,30
850,32
1004,17
1051,17
1093,41
1112,44
1176,02
1208,47
1333,14
1389,59
1371,09
1441,90
1479,22
1611,99
1700,92
2879,45
2927,28
2973,44
3102,30

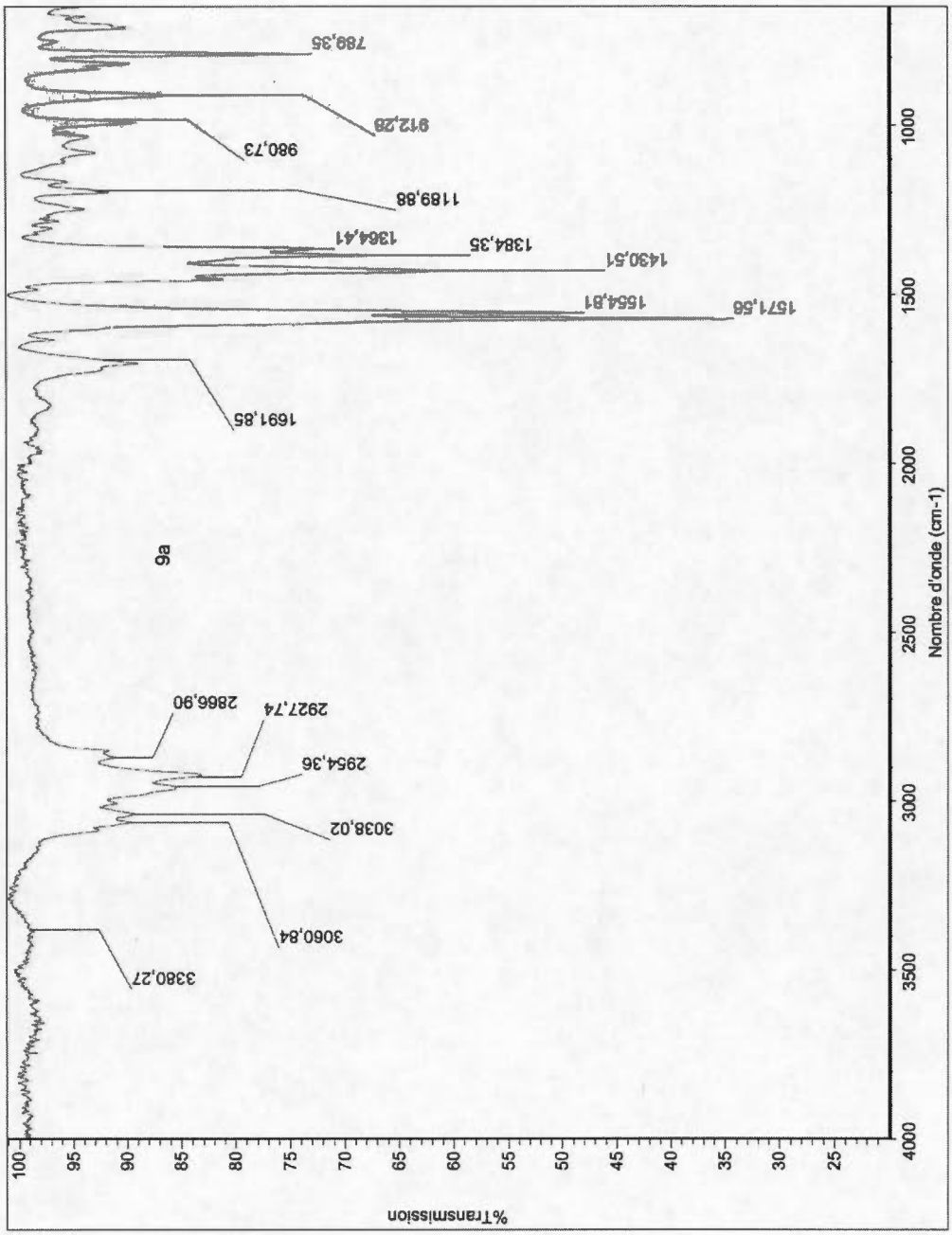

10.1529
10.1189
8.1600
8.1452
8.3838
8.3725
8.3694
8.3574
8.3536
8.2840
8.2769
8.2566
8.2495
7.9912
7.9880
7.9840
7.7087
7.6840
7.6584
2.00
1.02
1.02
1.01
1.08
2.02
1.08
7a

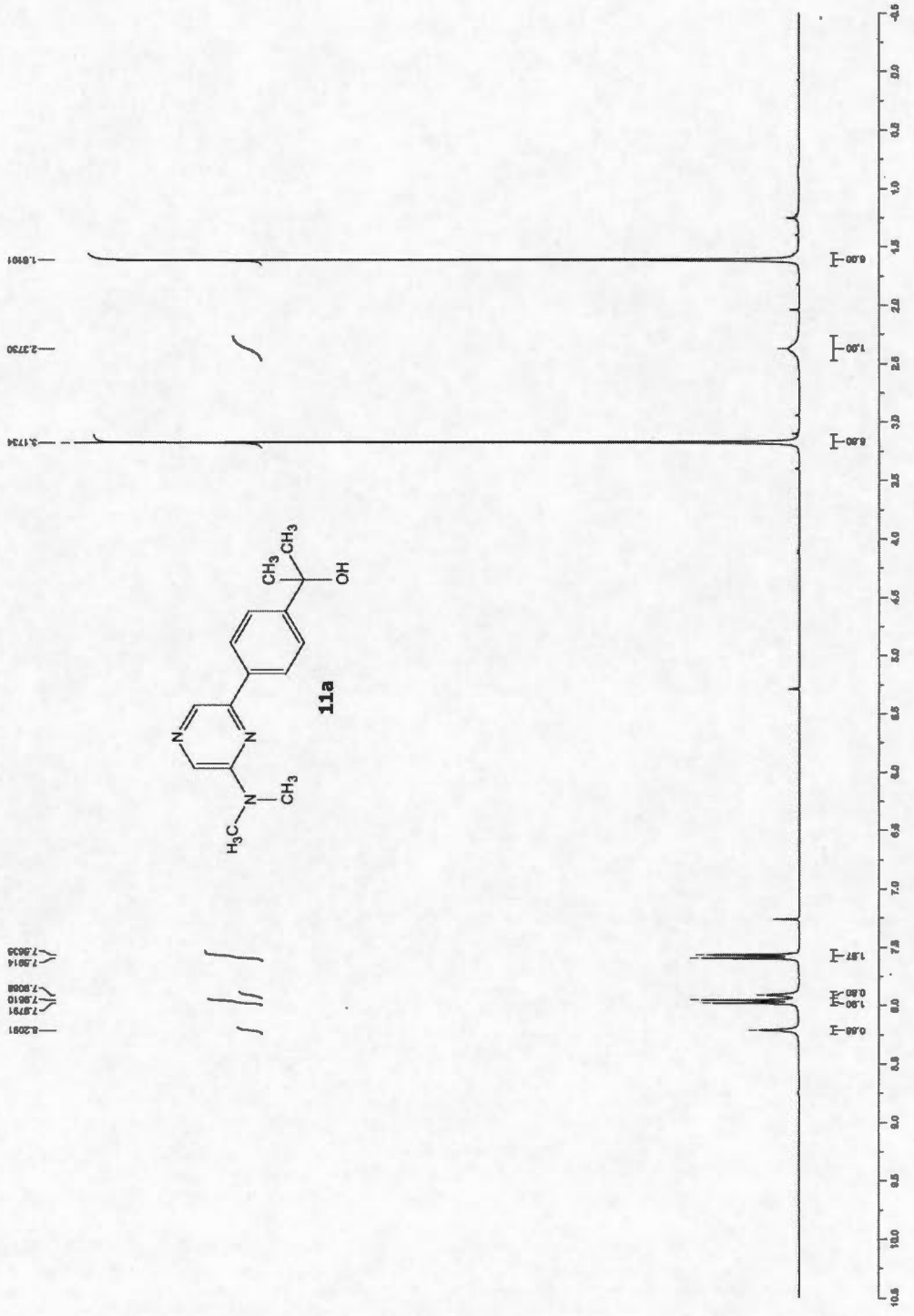

7a
191.9027
190.3186
182.3667
180.5723
136.9819
137.0918
136.8881
135.2860
131.1236
130.3820
129.8306
128.8264
120.7531

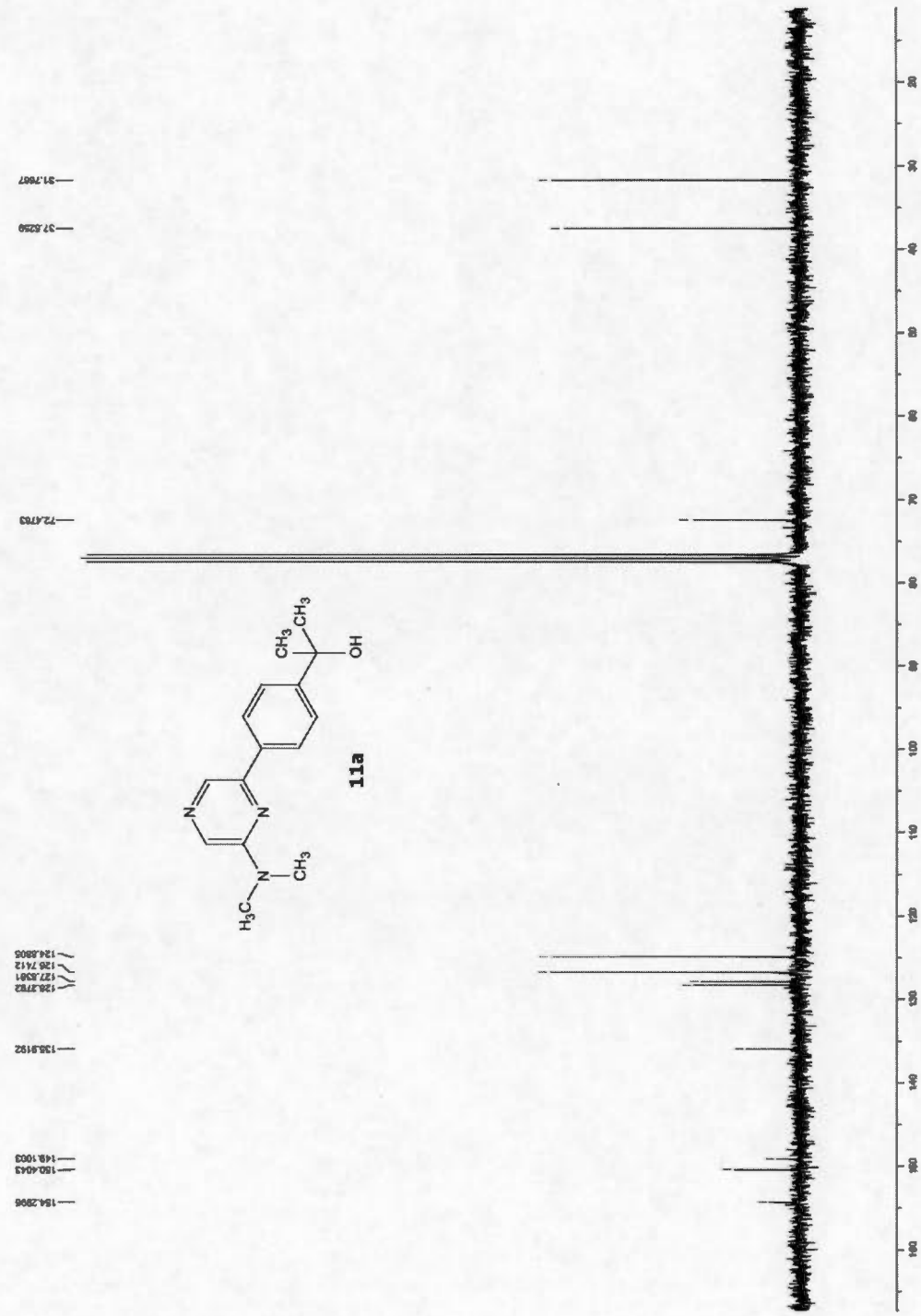

%Transmission
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
4000
3500
3000
2500
2000
1500
1000
Nombre d'onde (cm-1)
7a
3053,24
2851,69
2745,21
1689,41
1587,45
1359,28
1211,60
1183,16
1165,70
835,09
795,27
739,77

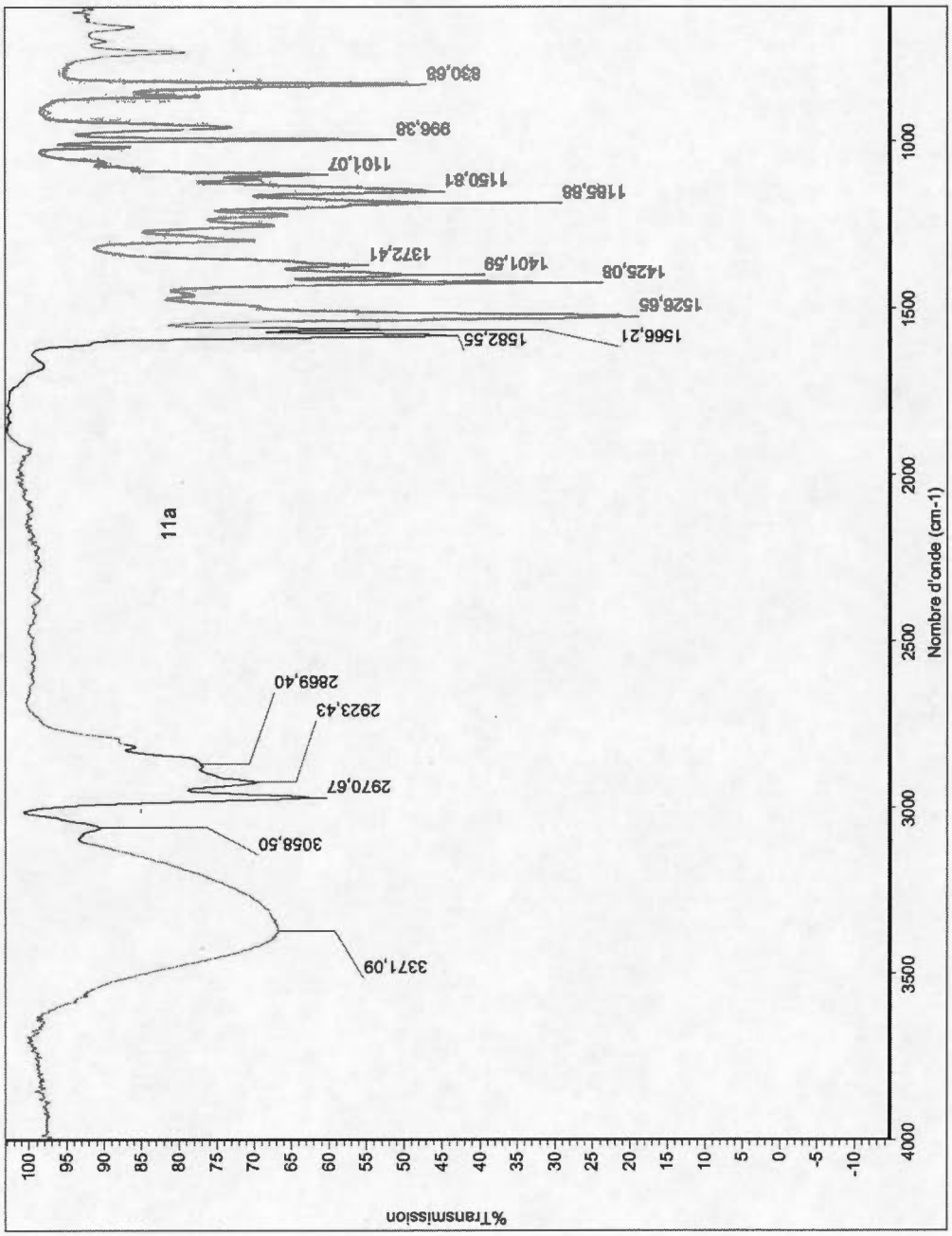

8.6612
8.6443
8.4896
8.4834
8.4772
8.3554
8.3503
8.3450
8.3296
8.3247
8.3196
7.5533
7.5330
7.5276
7.4723
7.4468
7.4210
7.2606
7.0673
7.0505
6.8761
6.8398
6.8175
6.7813
5.9079
5.9048
5.8499
5.8464
5.3284
5.3254
5.2925
5.2894
2.5988
1.00
1.00
0.99
1.09
1.19
1.01
1.08
1.10
1.14
3.01
9a
f1 (ppm)

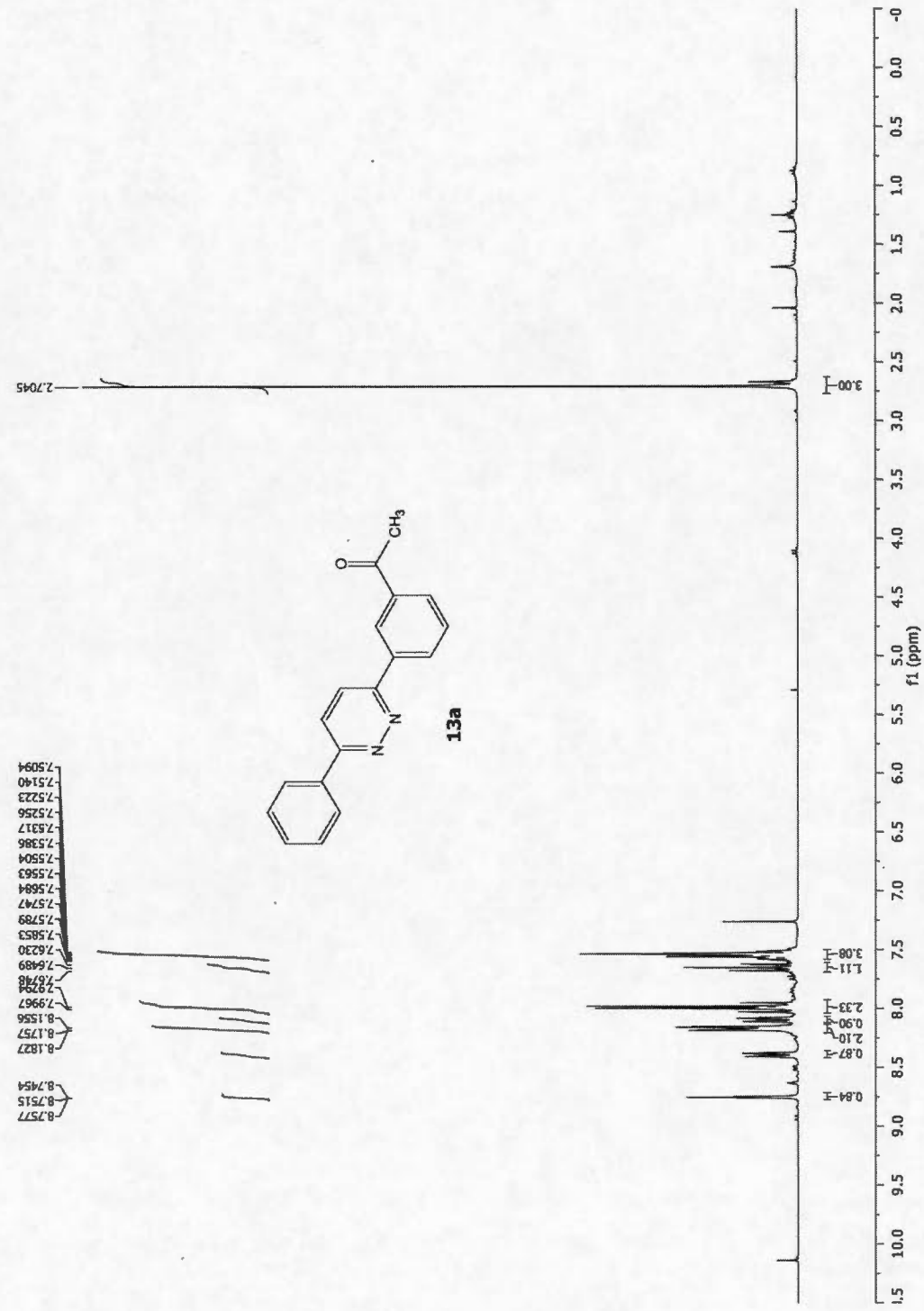

167.3398
164.2280
156.7920
138.0854
137.8922
136.7061
128.7578
128.1474
127.6395
126.1829
118.7404
114.3102
24.4606
H3C
N
N
CH2
9a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

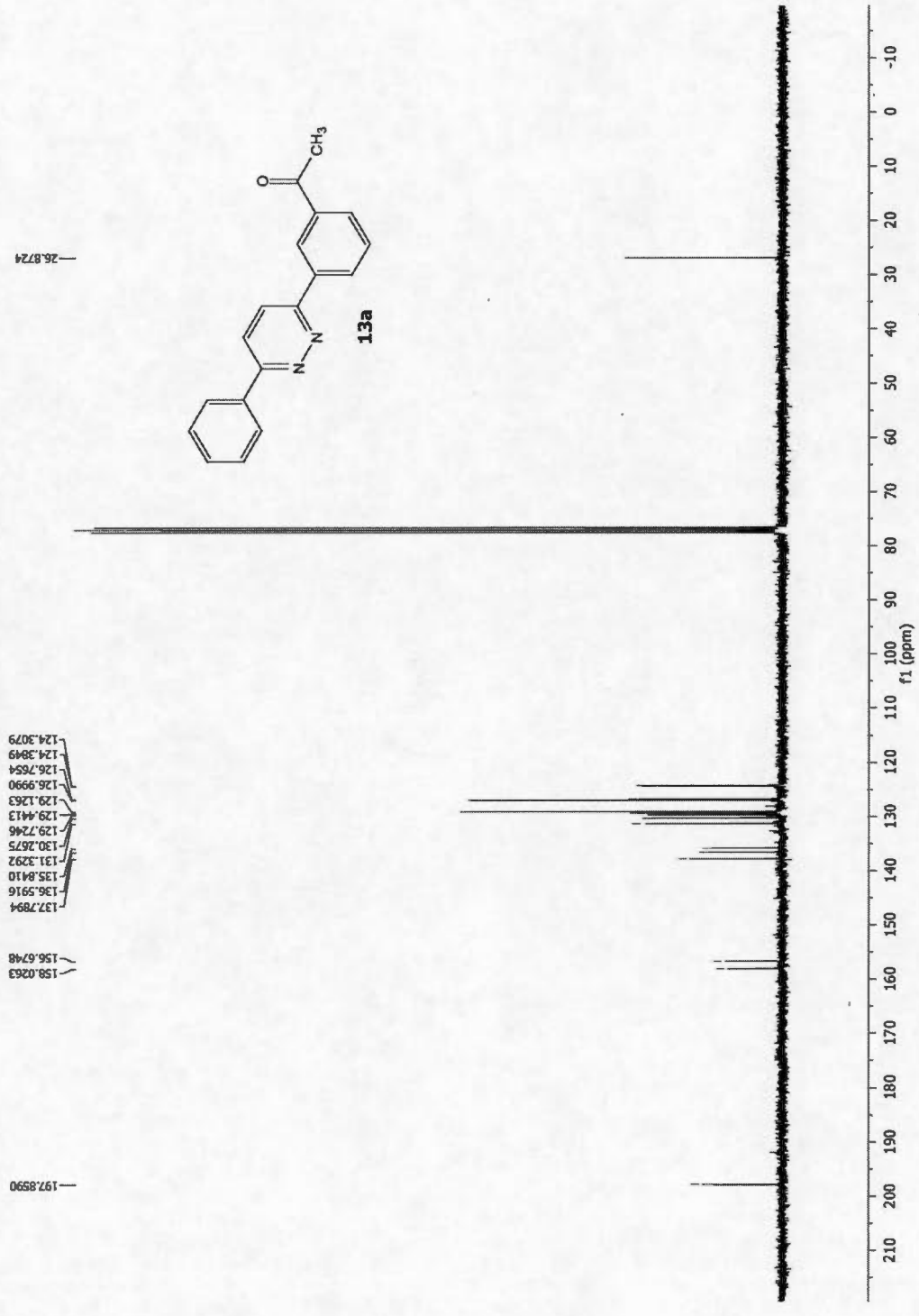

%Transmission
Nombre d'onde (cm-1)
9a
3380,27
3060,84
3038,02
2954,36
2927,74
2866,90
1691,85
1571,56
1554,81
1430,51
1384,35
1364,41
1189,88
980,73
912,28
789,35

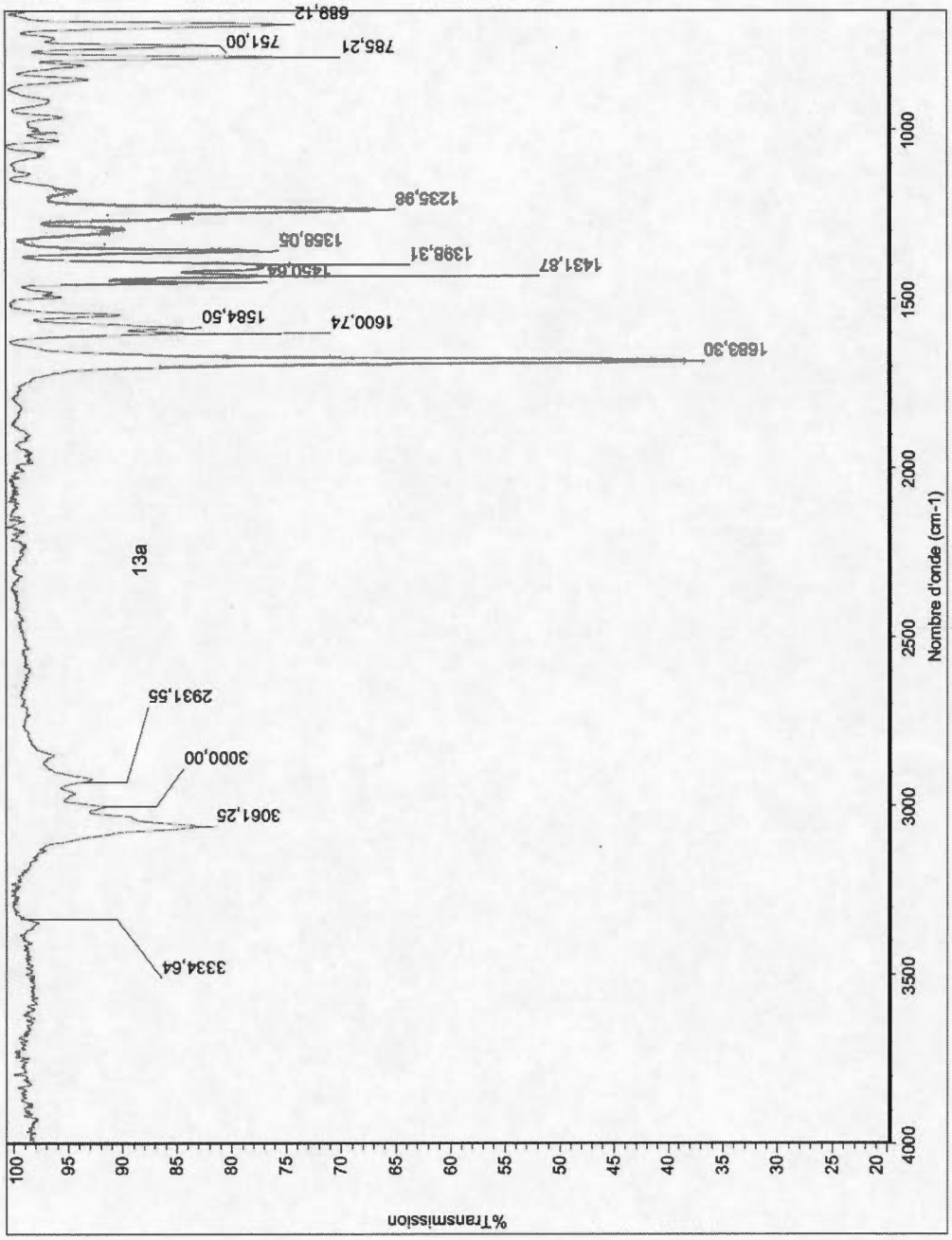

11a

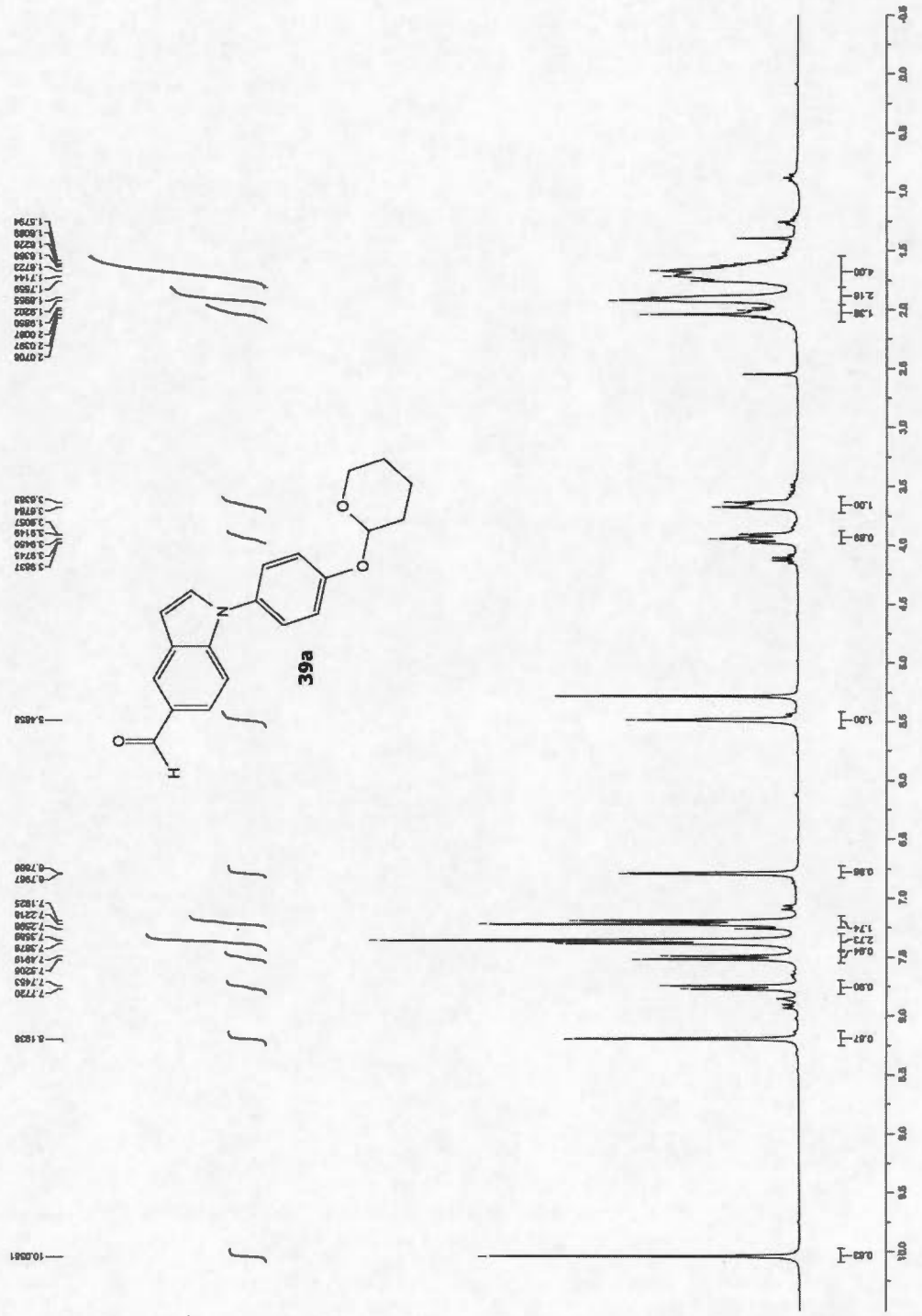

31.7667
37.8259
72.4783
128.3782
127.8361
126.7412
124.8805
135.8192
154.2906
150.4043
148.1003
11a

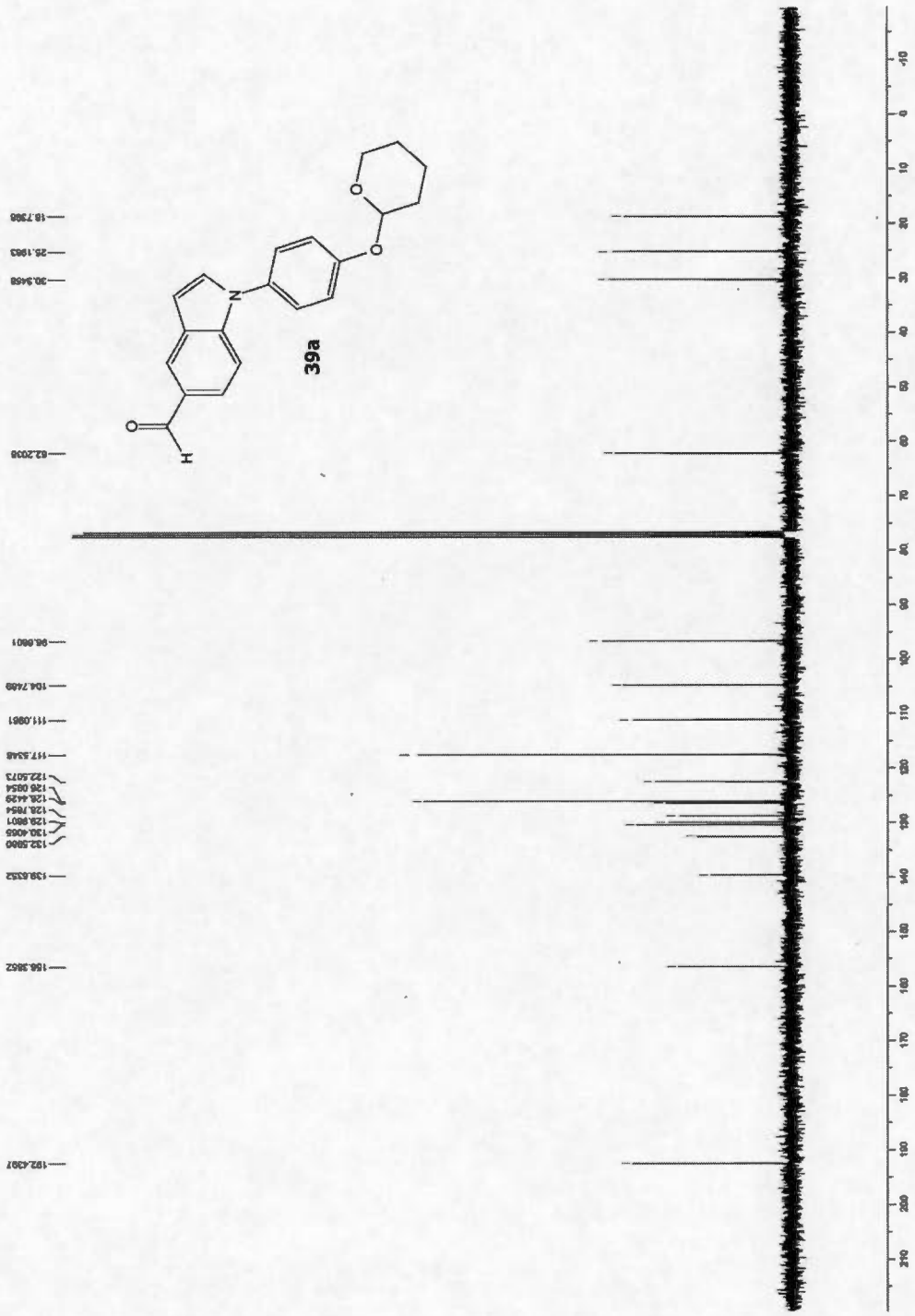

%Transmission
Nombre d'onde (cm-1)
11a
3371,09
3058,50
2970,67
2923,43
2869,40
1582,55
1566,21
1526,65
1425,08
1401,58
1372,41
1185,88
1150,81
1101,07
996,38
830,68

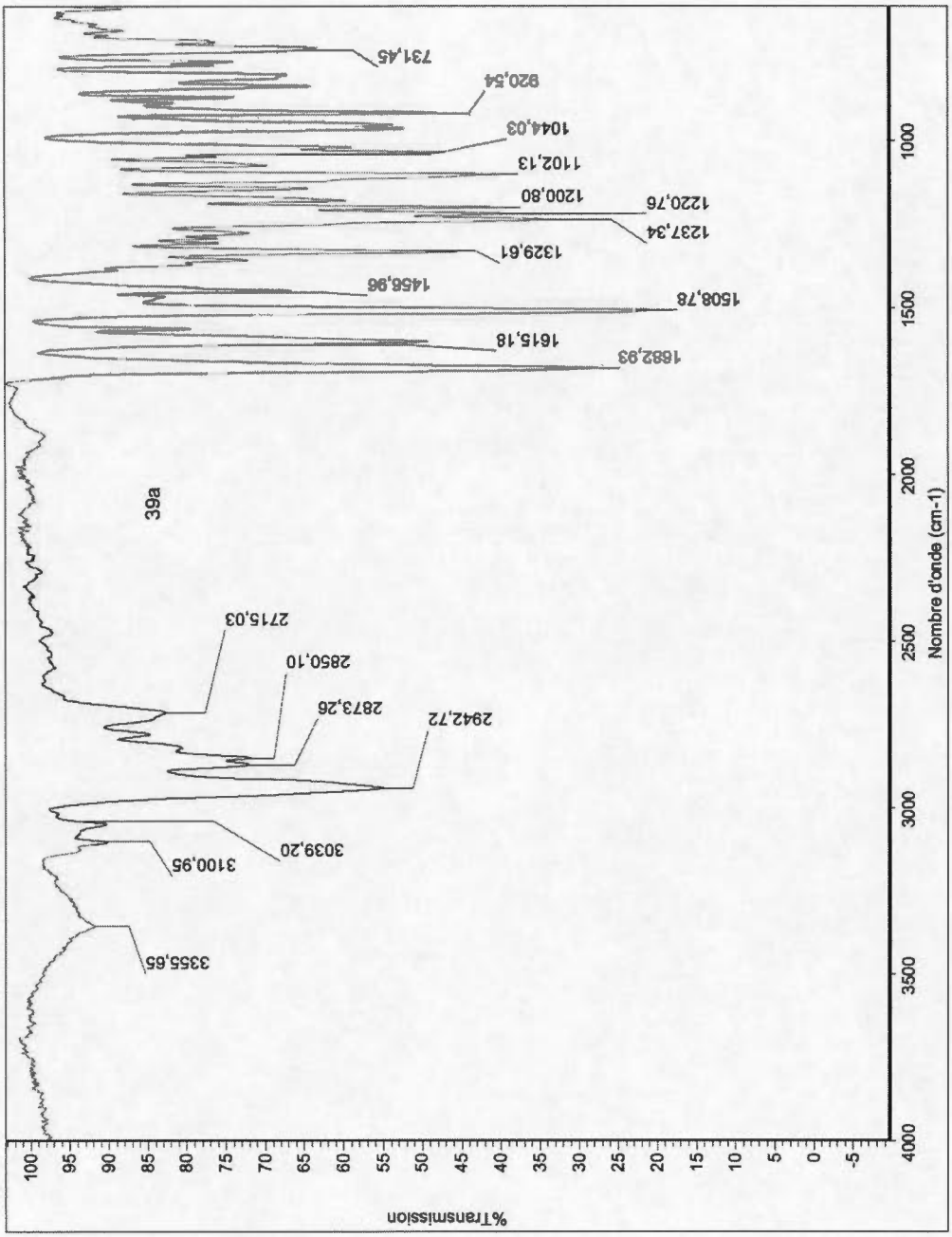

13a
f1 (ppm)

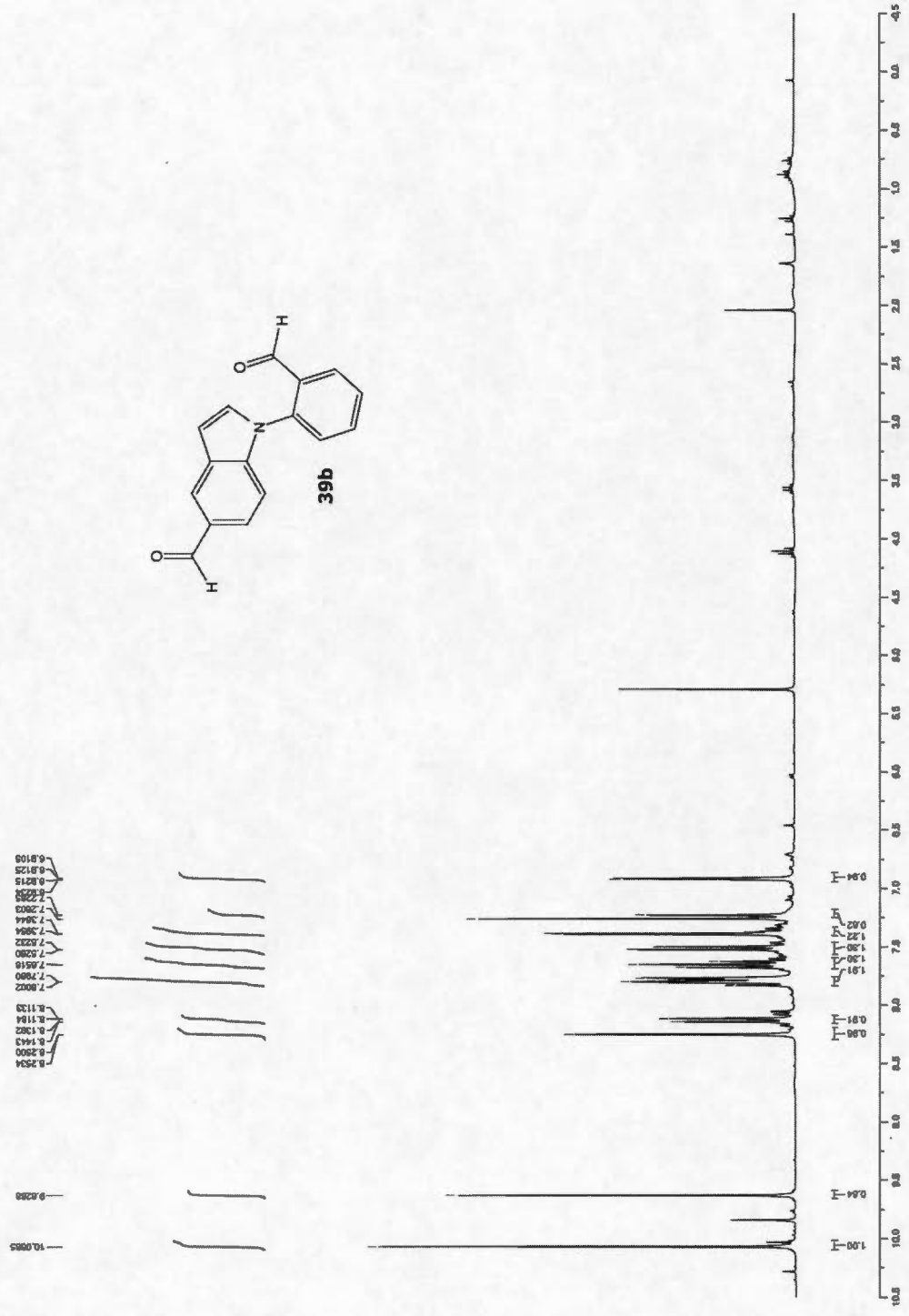

26.8724
197.8590
158.0263
156.6748
137.7894
136.5916
135.8410
131.3292
130.2675
129.7246
129.4413
129.1263
126.9990
126.7654
124.3849
124.3079
13a
f1 (ppm)

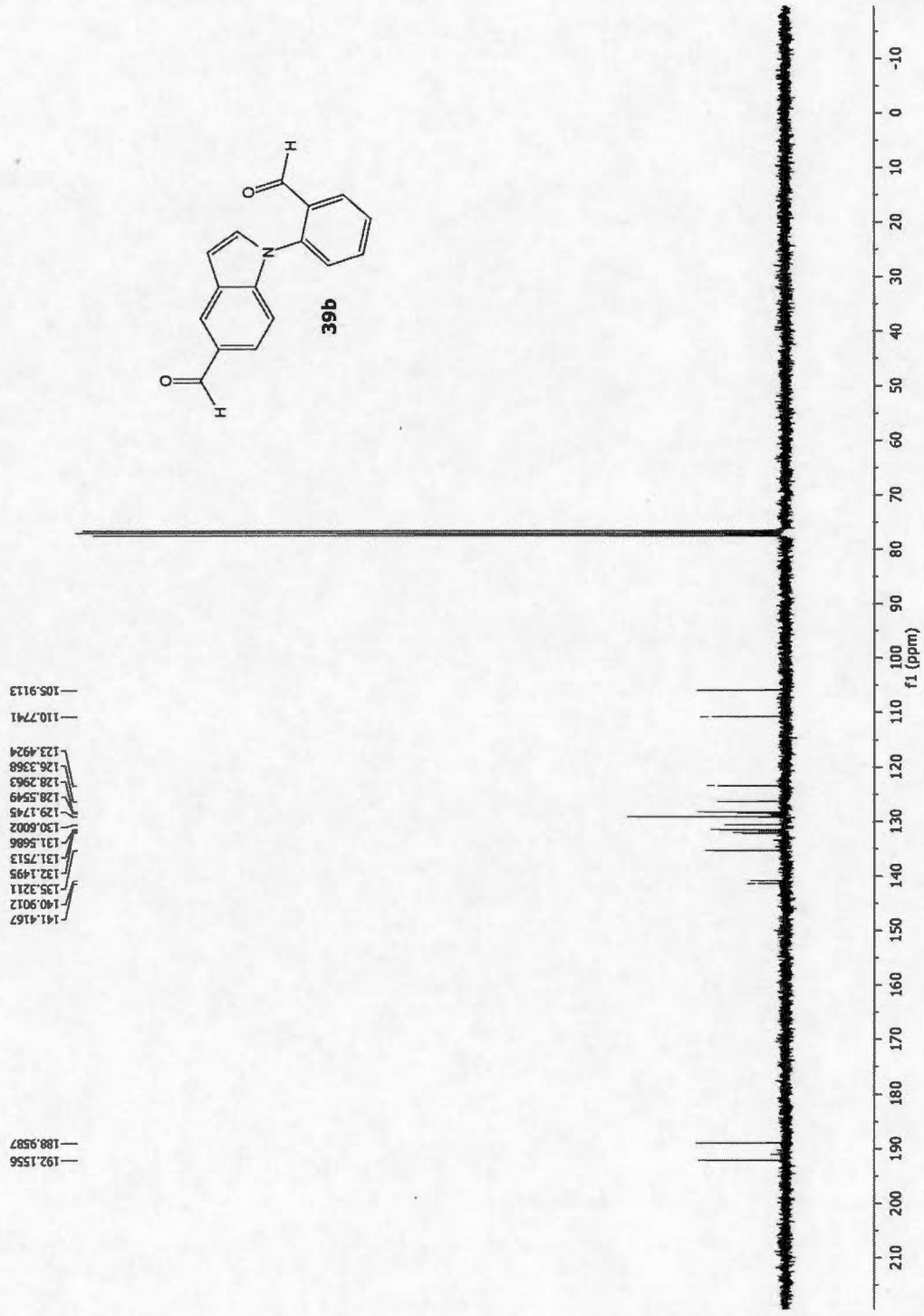

%Transmission
Nombre d'onde (cm-1)
13a
3334,64
3061,25
3000,00
2931,55
1683,30
1600,74
1584,50
1450,64
1431,87
1398,31
1358,05
1235,98
785,21
751,00
688,12

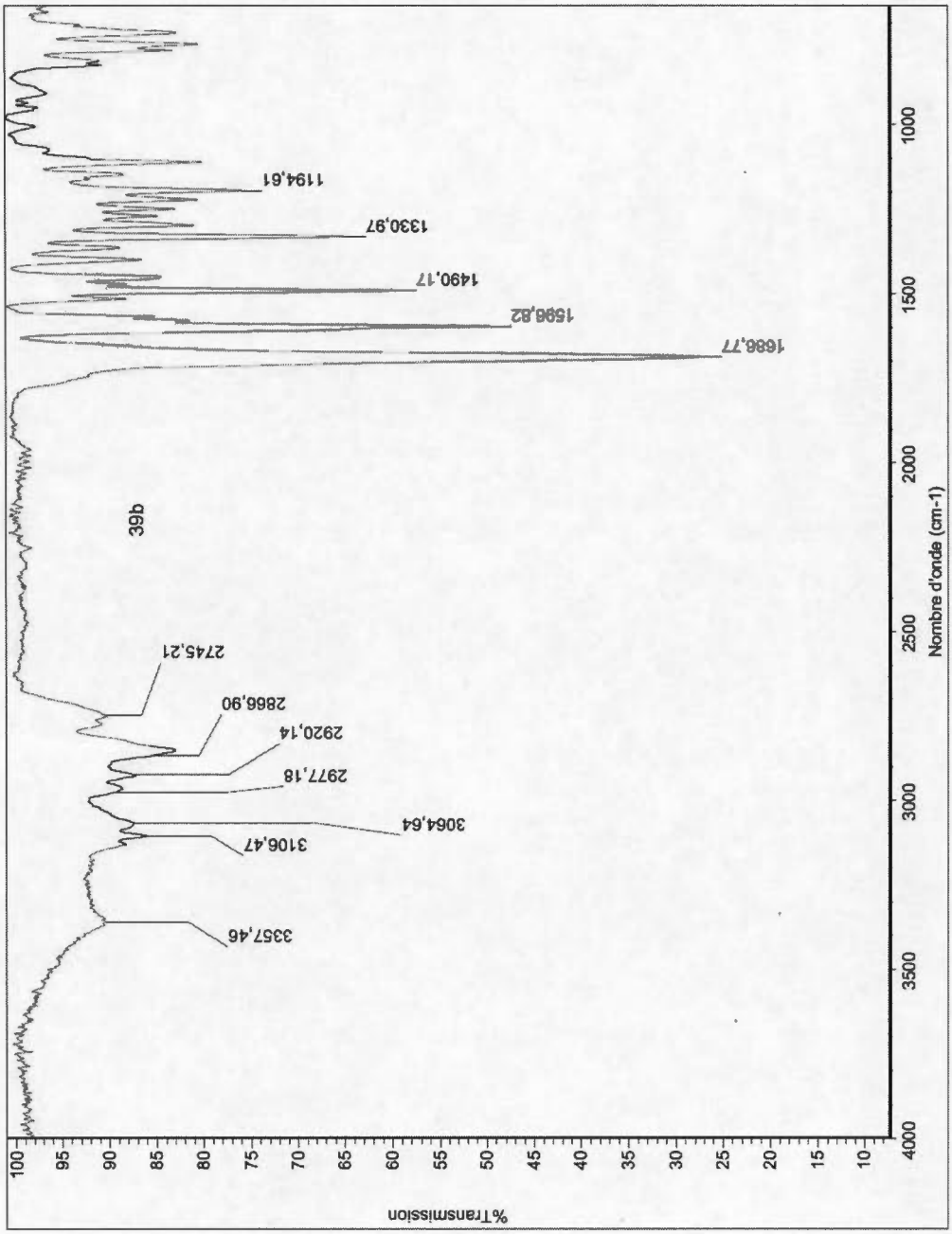

39a

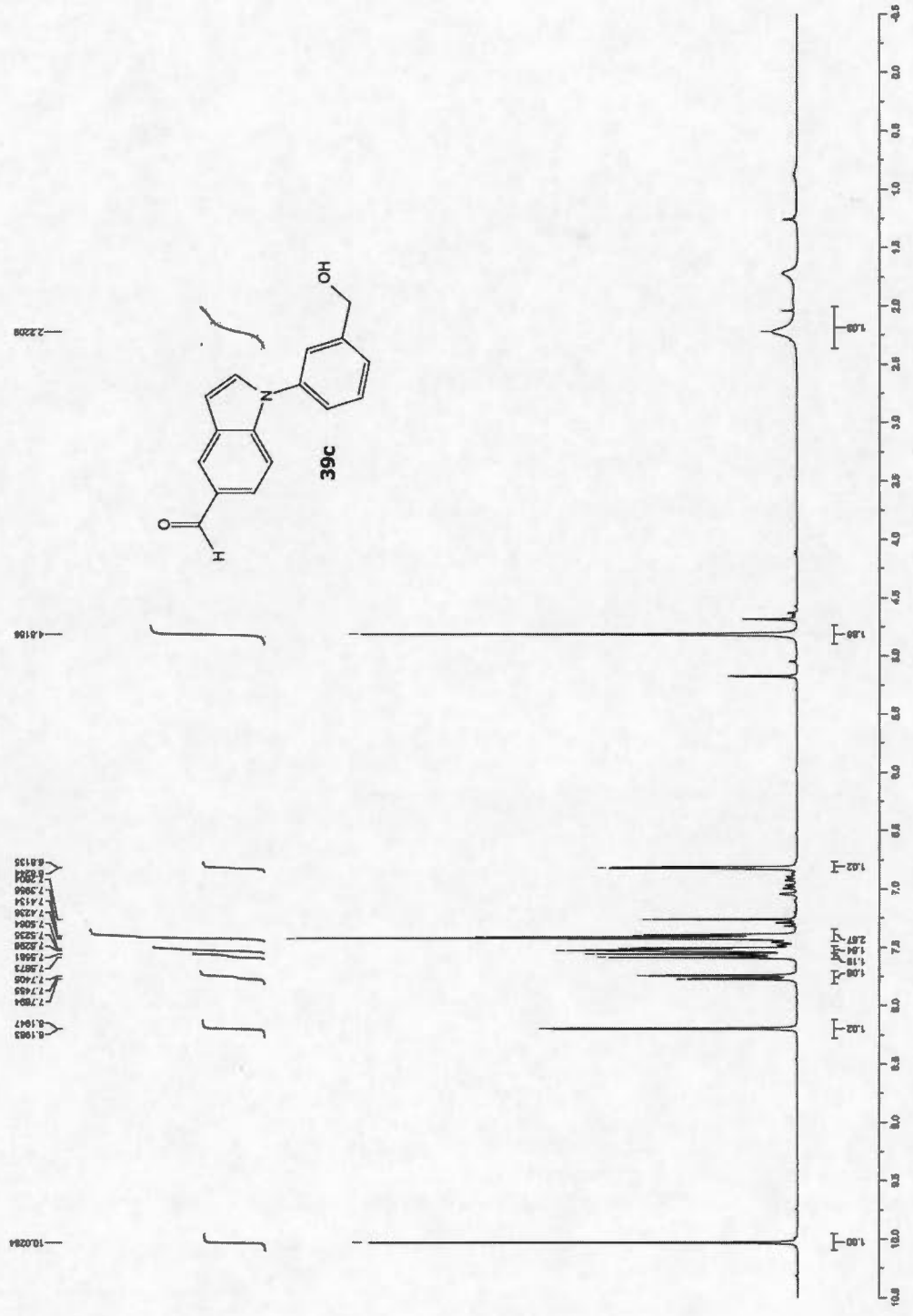

18.7366
25.1963
30.3468
62.2036
86.6801
104.7489
111.0861
117.5348
122.5073
126.0854
126.4139
128.7954
129.8601
130.4065
132.5960
139.6352
156.3862
182.4397
39a

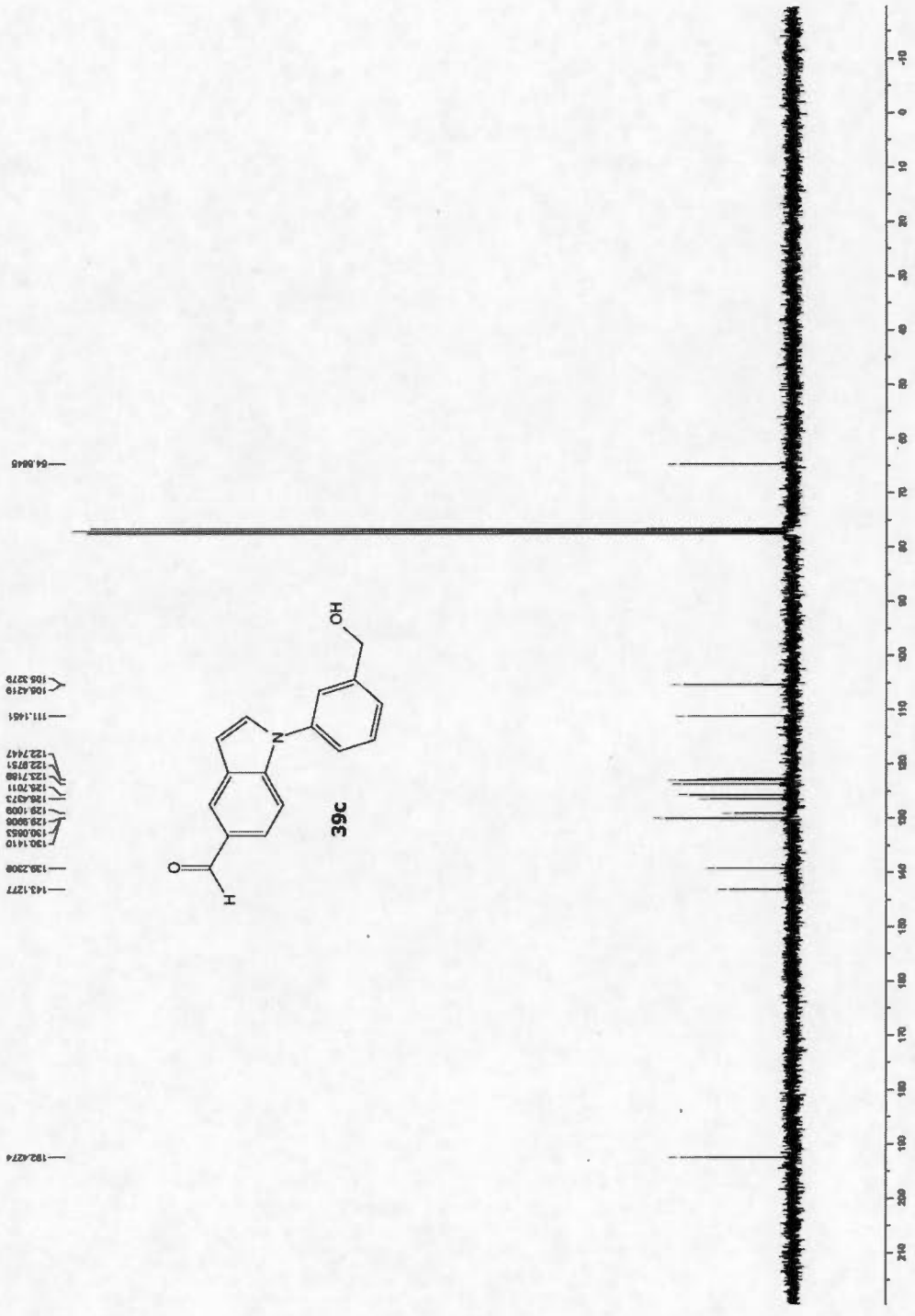

%Transmission
Nombre d'onde (cm-1)
39a
3355,65
3100,95
3039,20
2942,72
2873,26
2850,10
2715,03
1682,93
1615,18
1508,78
1456,96
1329,61
1237,34
1220,76
1200,80
1102,13
1044,03
820,54
731,45

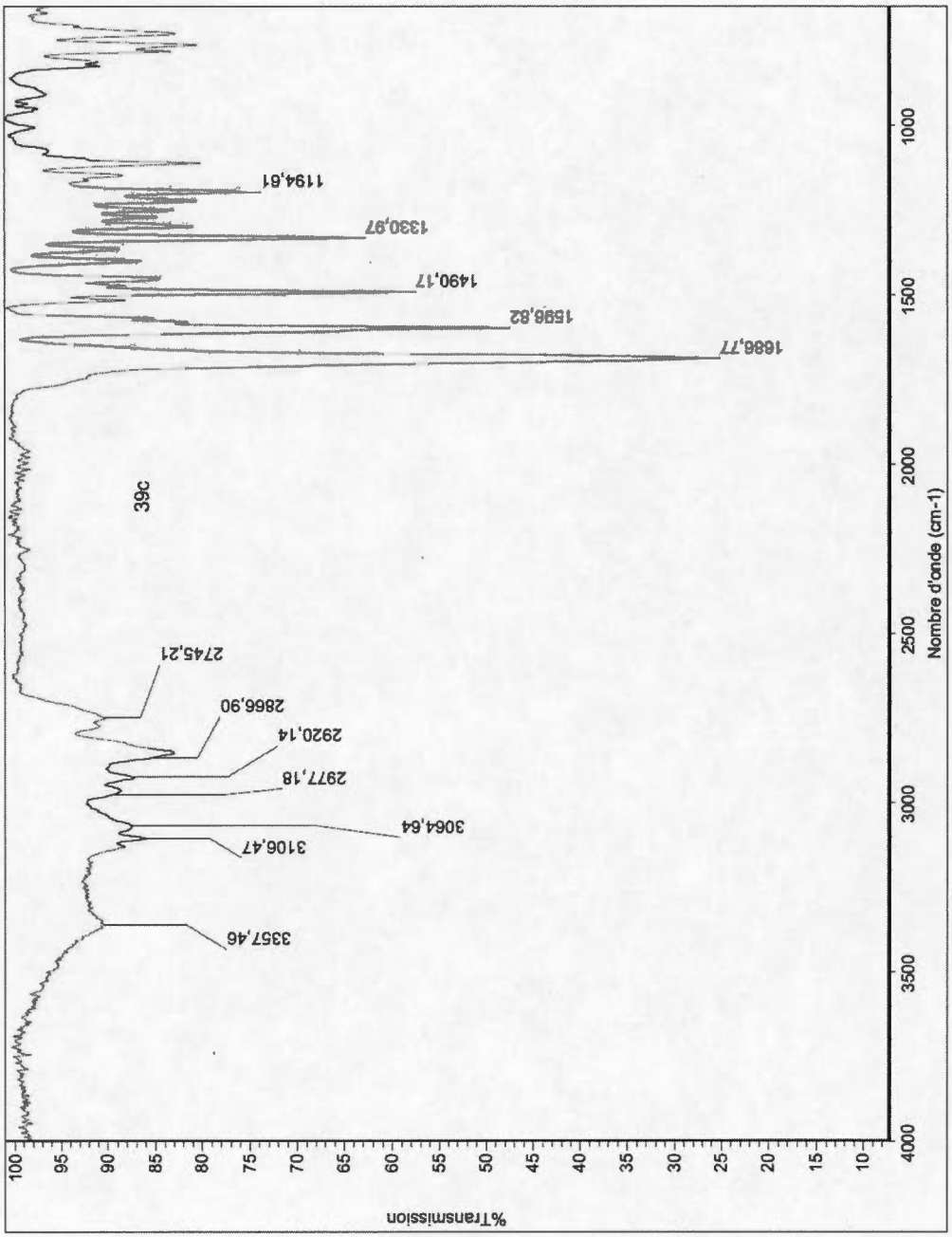

39b

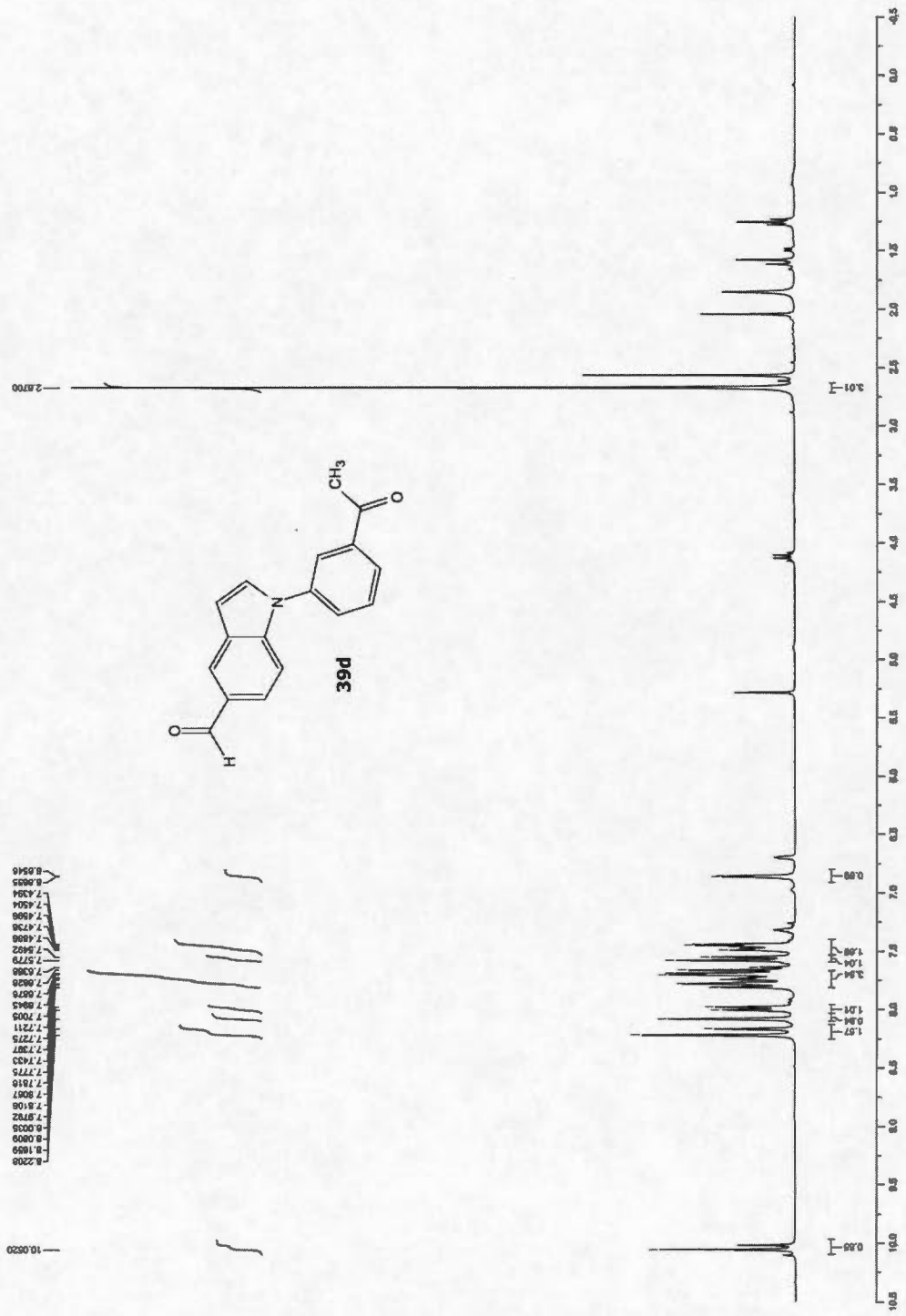

39b
f1 (ppm)
192.1556
188.9587
141.4167
140.9012
135.3211
132.1495
131.7513
131.5686
130.6002
129.1745
128.5549
128.2963
126.3368
123.4924
110.7741
105.9113

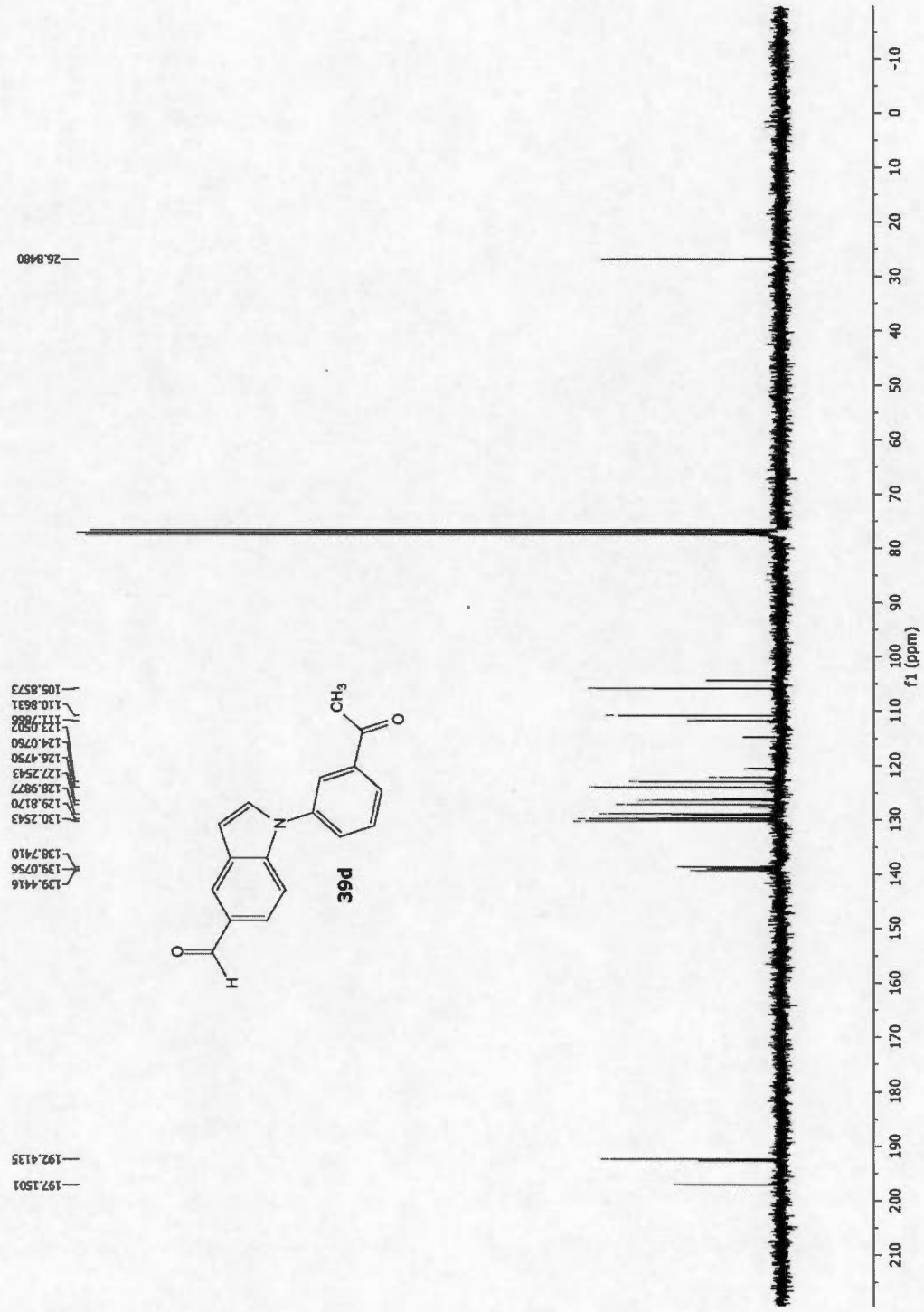

%Transmission
Nombre d'onde (cm-1)
39b
3357,46
3106,47
3064,64
2977,18
2920,14
2866,90
2745,21
1686,77
1596,82
1490,17
1330,97
1194,61

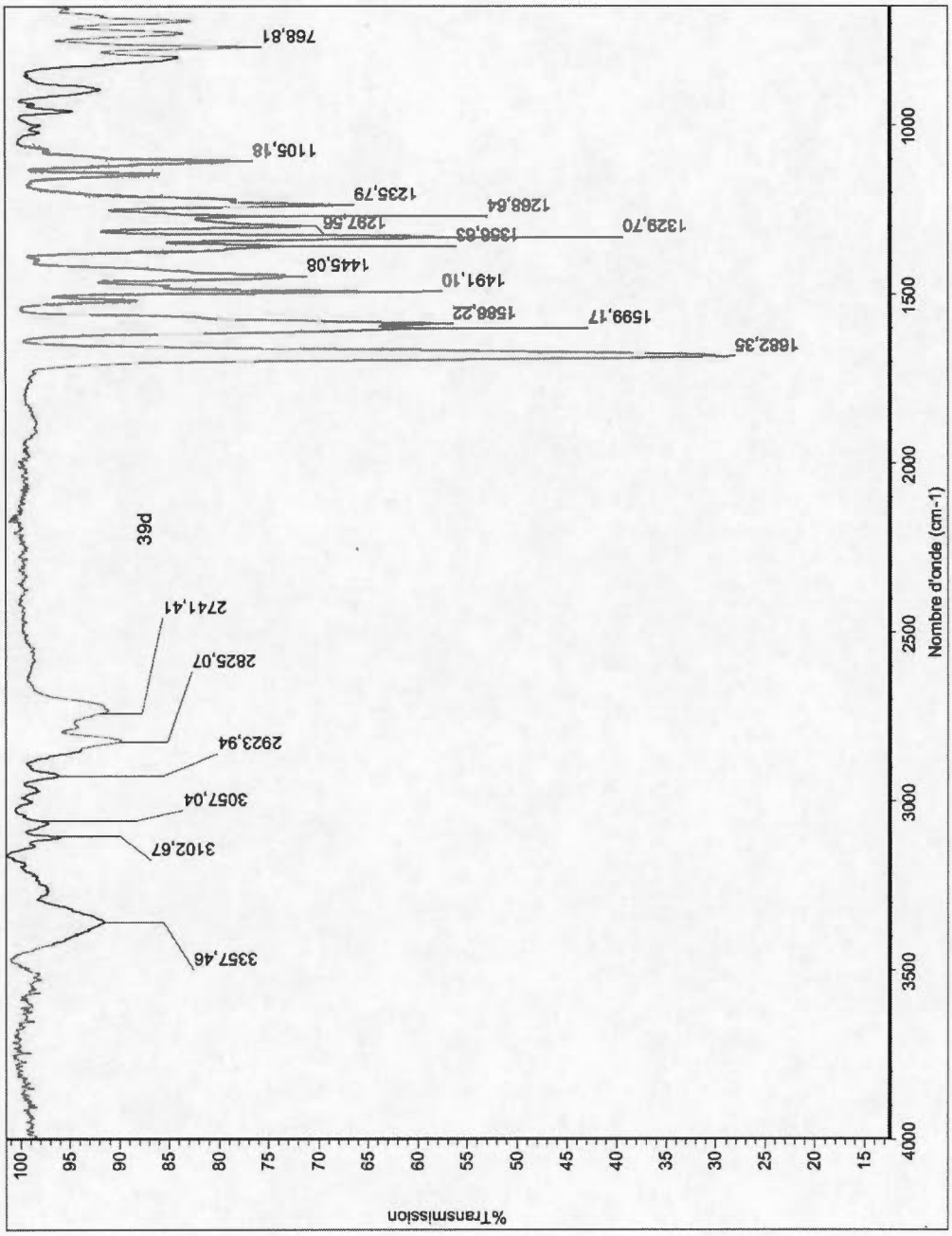

39c
OH
N
O
H


182.4274
143.1277
139.2308
130.1410
130.0053
129.9006
129.1069
128.4373
125.7011
123.7188
122.8751
122.7447
111.1461
106.4219
105.3279
64.8845
39c
OH
N
O
H

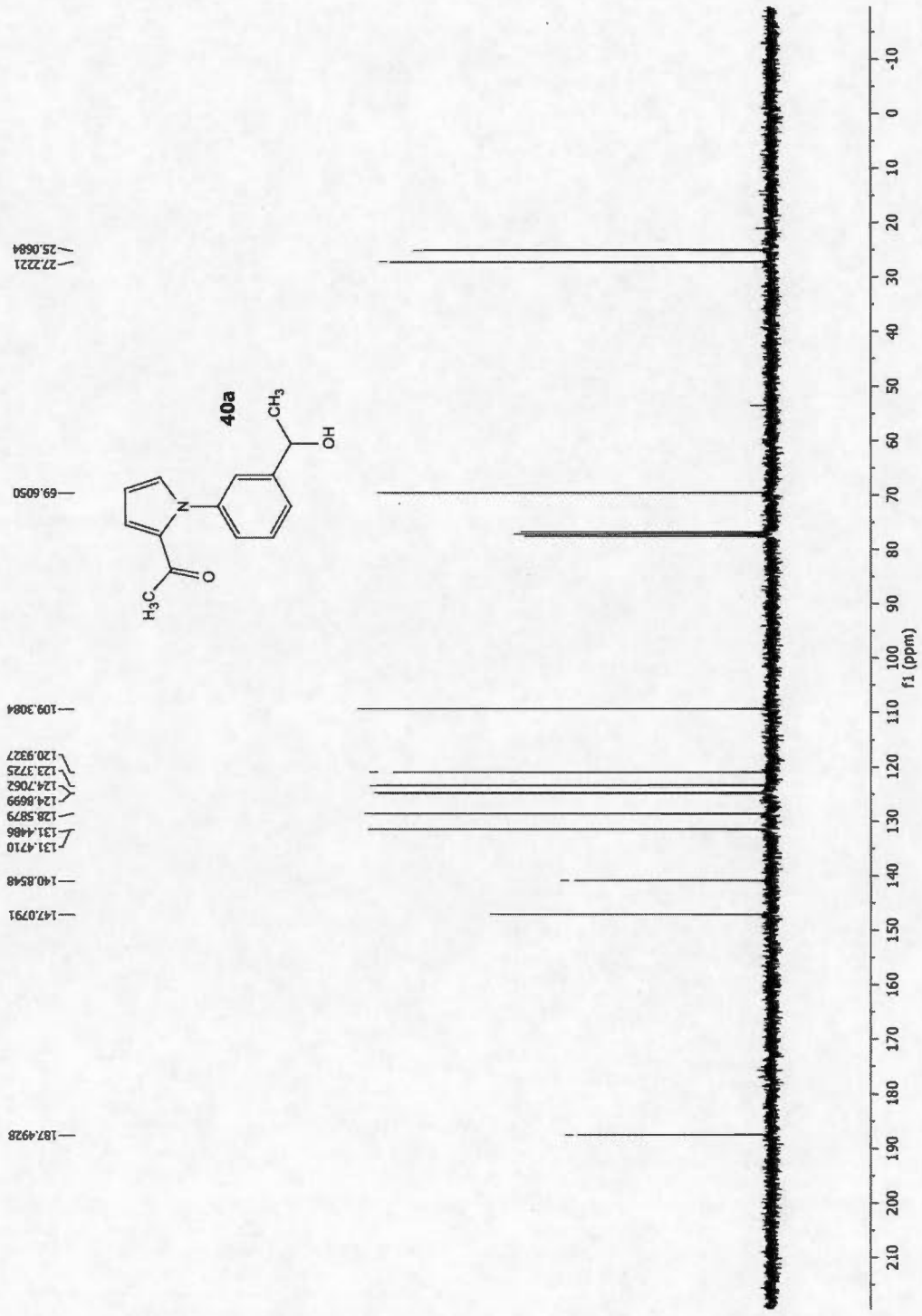

%Transmission
Nombre d'onde (cm-1)
39c
3357,46
3106,47
3064,64
2977,18
2920,14
2866,90
2745,21
1686,77
1596,82
1490,17
1330,97
1194,61

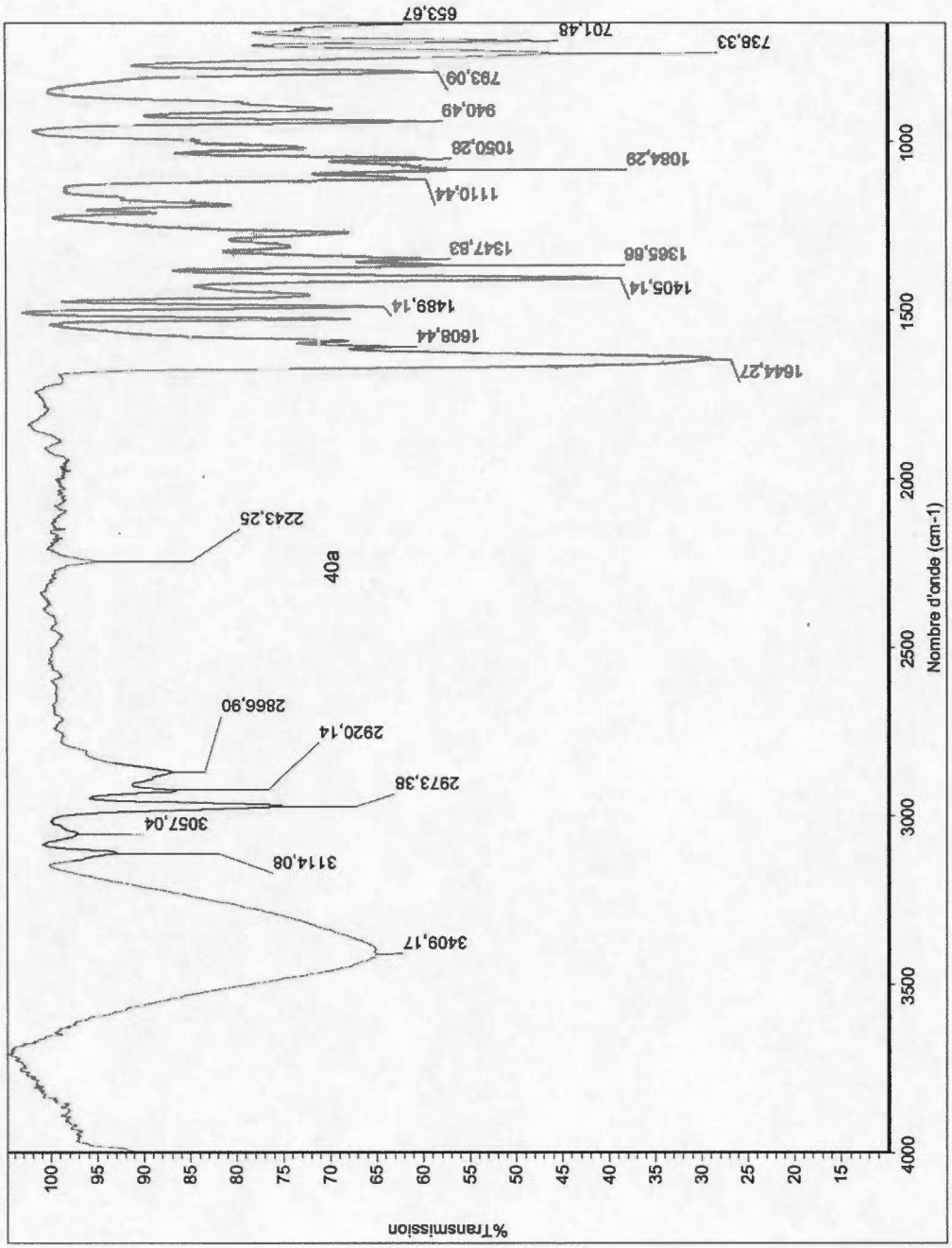

39d

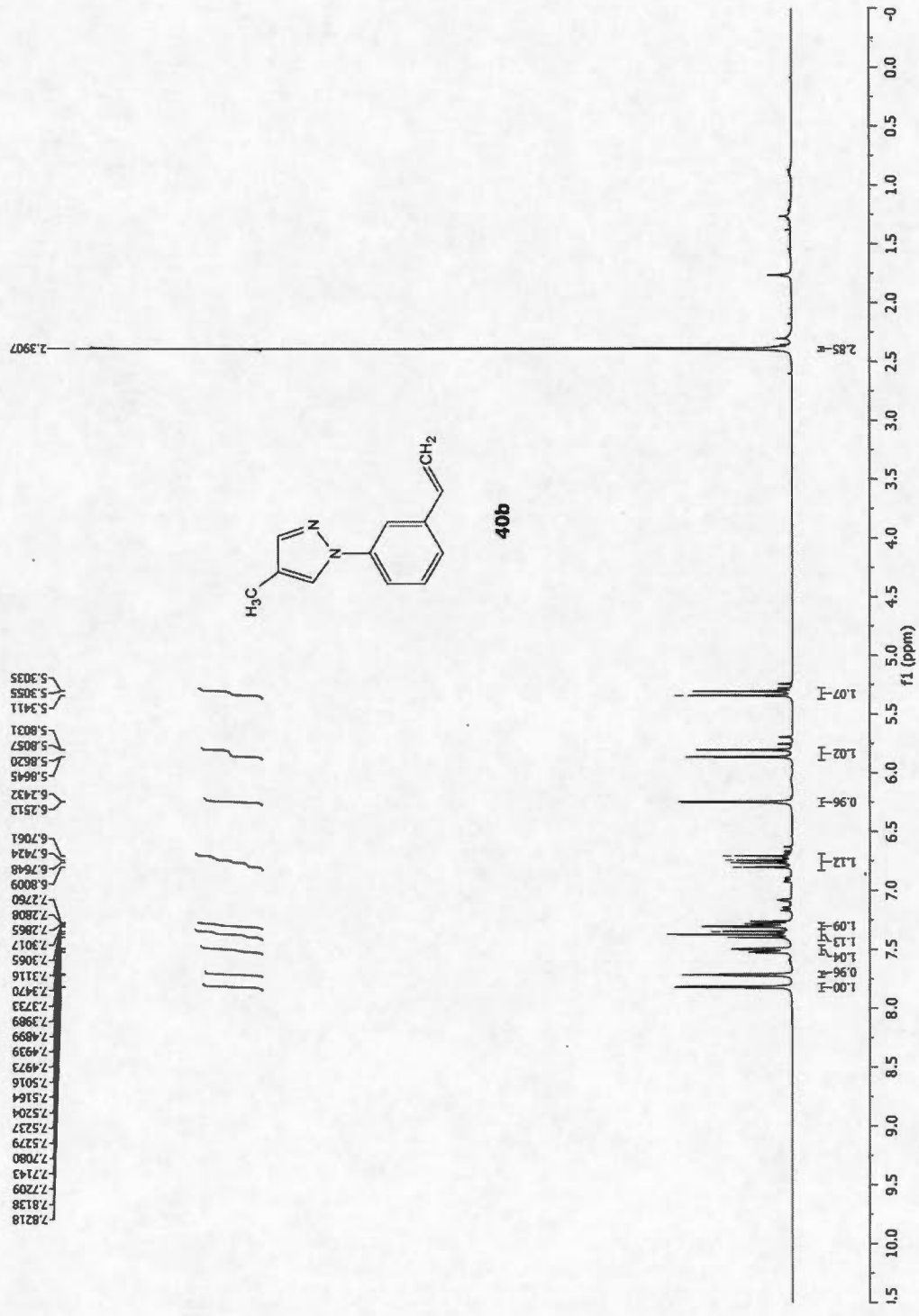

26.8480
192.4135
197.1501
105.8573
110.8631
111.7886
123.0802
124.0760
126.4750
127.2543
128.9877
129.8170
130.2543
138.7410
139.0756
139.4416
39d
f1 (ppm)

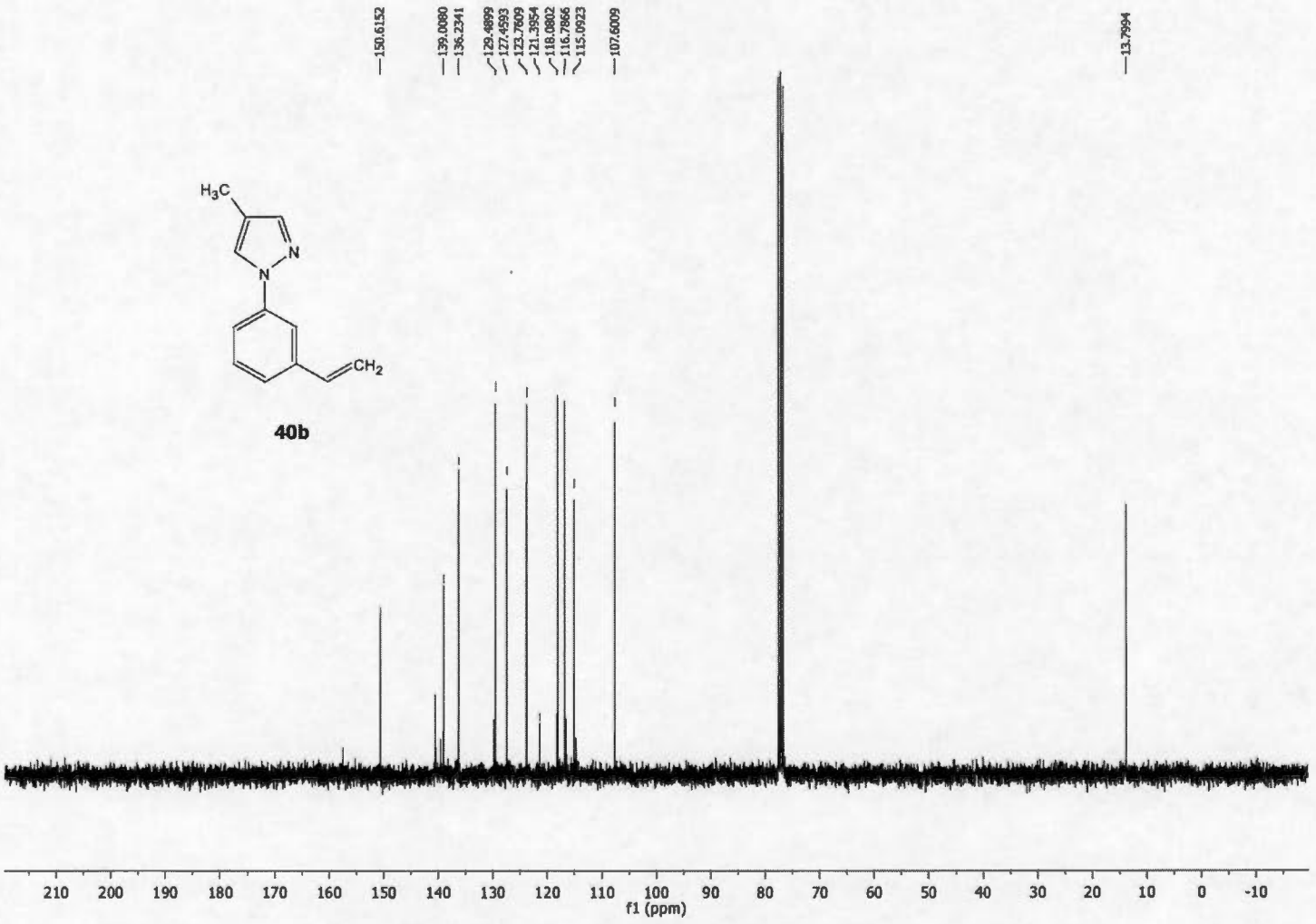

%Transmission
Nombre d'onde (cm-1)
39d
3357,46
3102,67
3057,04
2923,94
2825,07
2741,41
1682,35
1599,17
1586,22
1491,10
1445,08
1356,83
1329,70
1297,56
1268,64
1235,79
1105,18
768,81

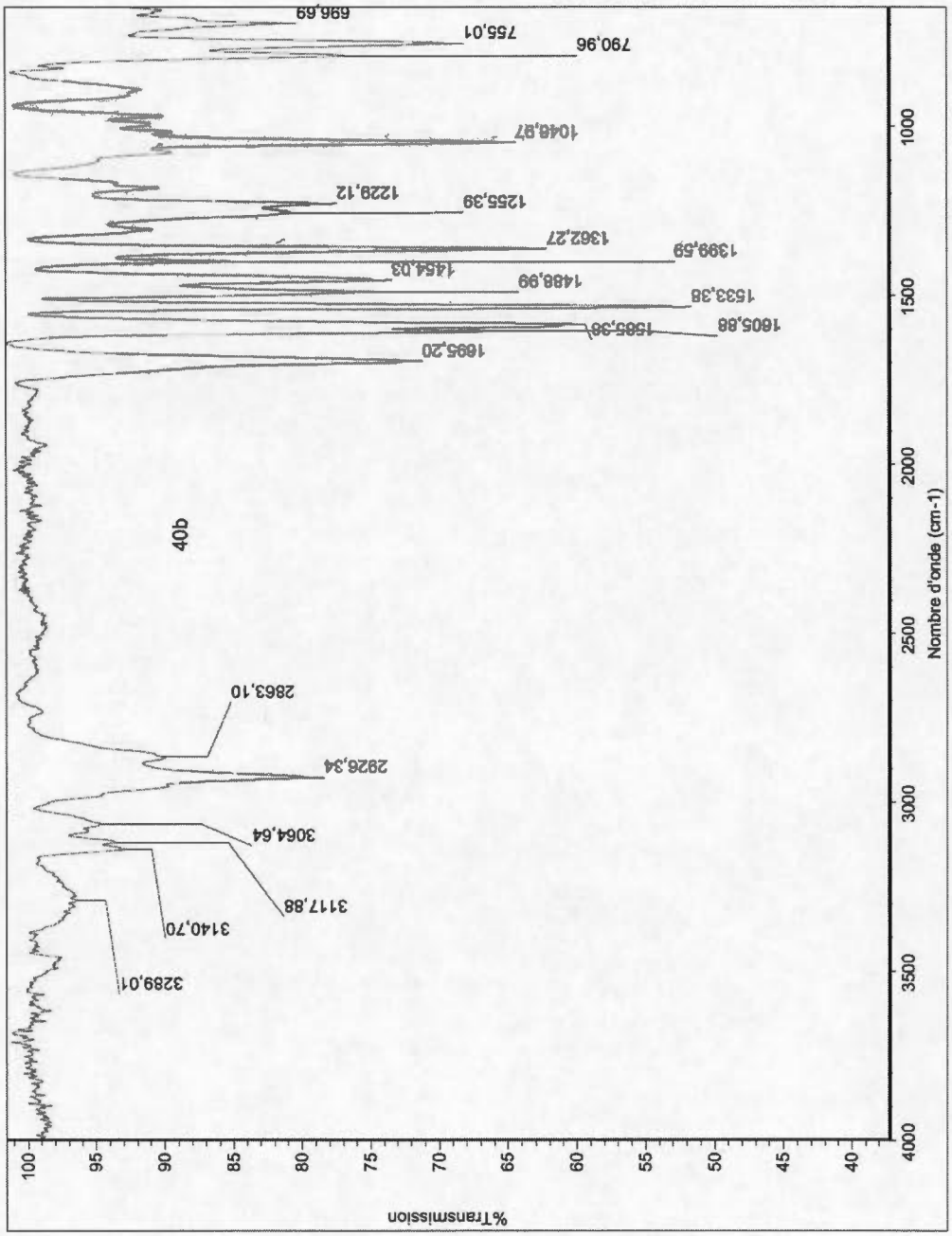
40a
f1 (ppm)

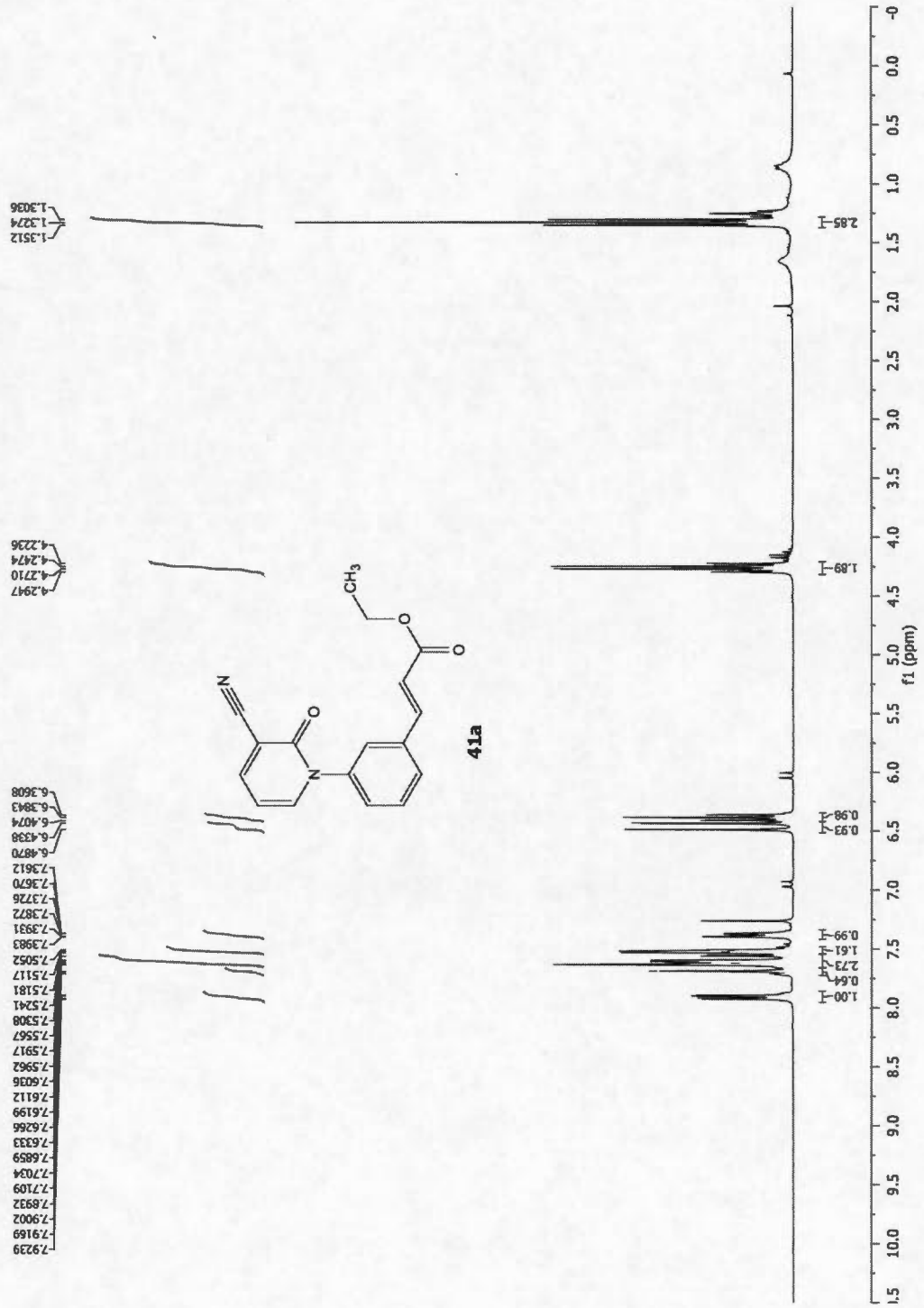

40a
CH3
OH
N
O
H3C
187.4928
147.0791
140.8548
131.4710
131.4486
128.5879
124.8699
124.7062
123.3725
120.9327
109.3084
69.6050
27.2221
25.0684
f1 (ppm)


%Transmission
Nombre d'onde (cm-1)
40a
3409,17
3114,08
3057,04
2973,38
2920,14
2866,90
2243,25
1644,27
1608,44
1489,14
1405,14
1365,66
1347,83
1110,44
1084,28
1050,28
940,49
793,09
738,33
701,48
653,67

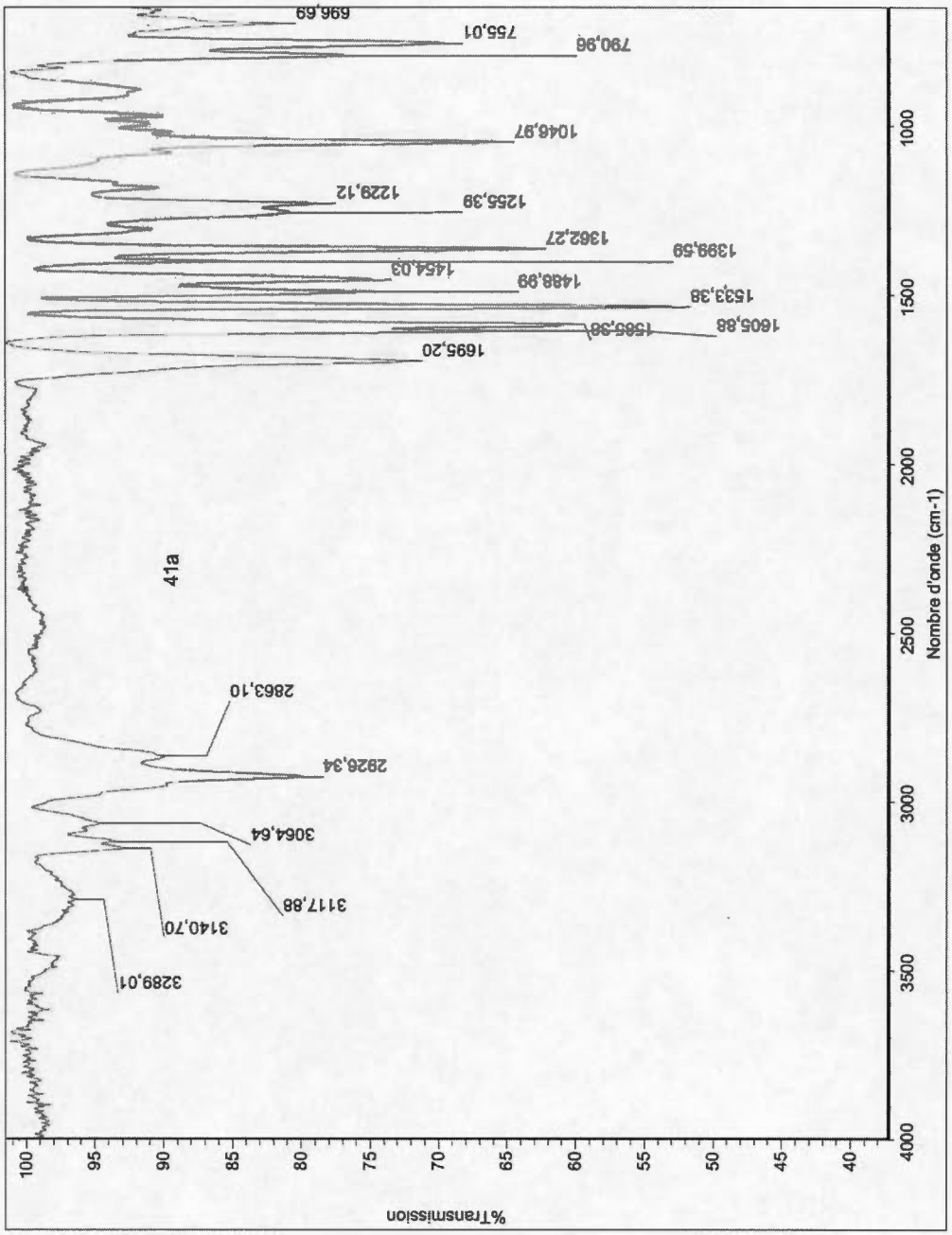

40b
f1 (ppm)

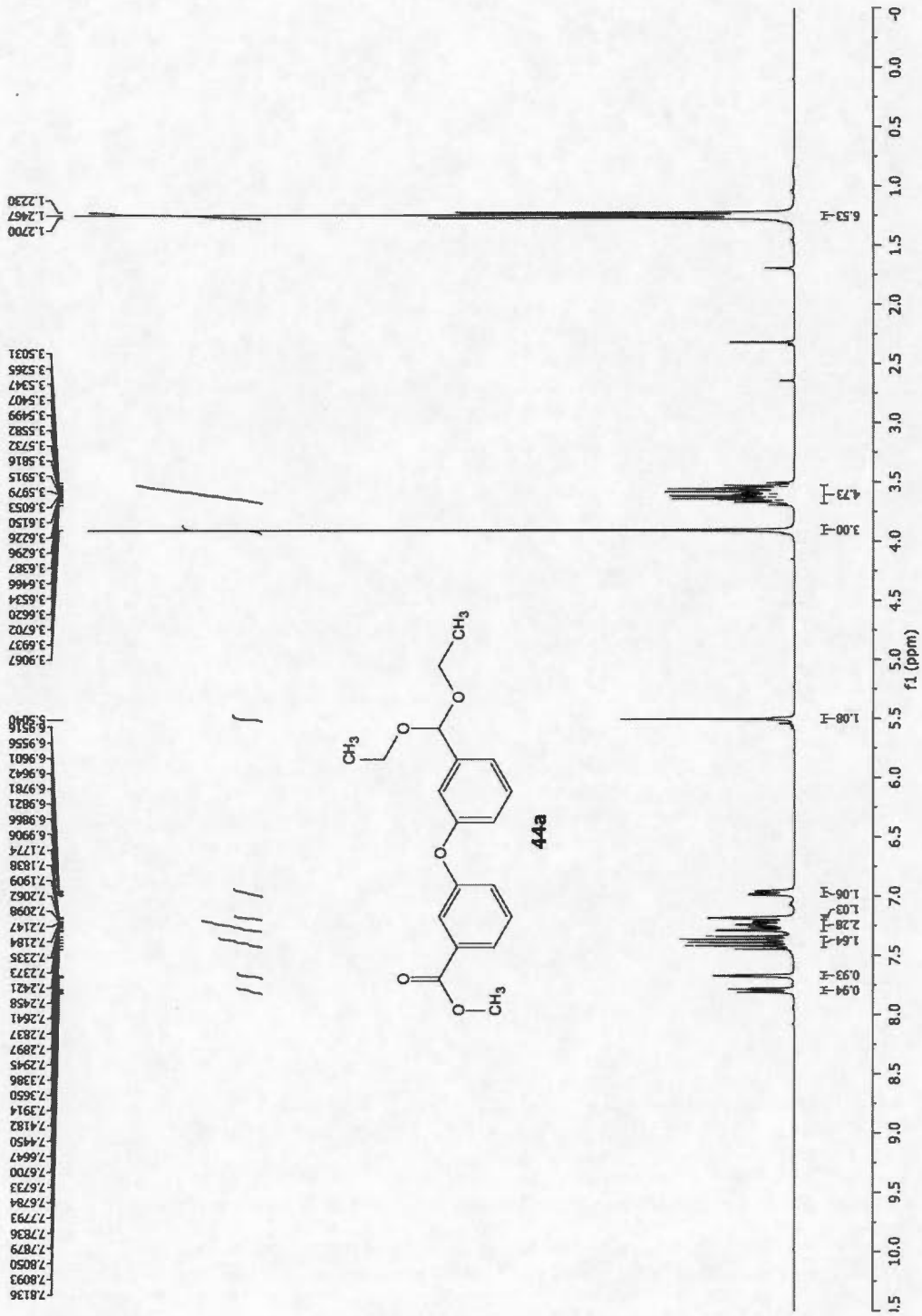

150.6152
139.0080
136.2341
129.4899
127.4593
123.7609
121.3954
118.0802
116.7866
115.0923
107.6009
13.7994
H3C
N
N
CH2
40b
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

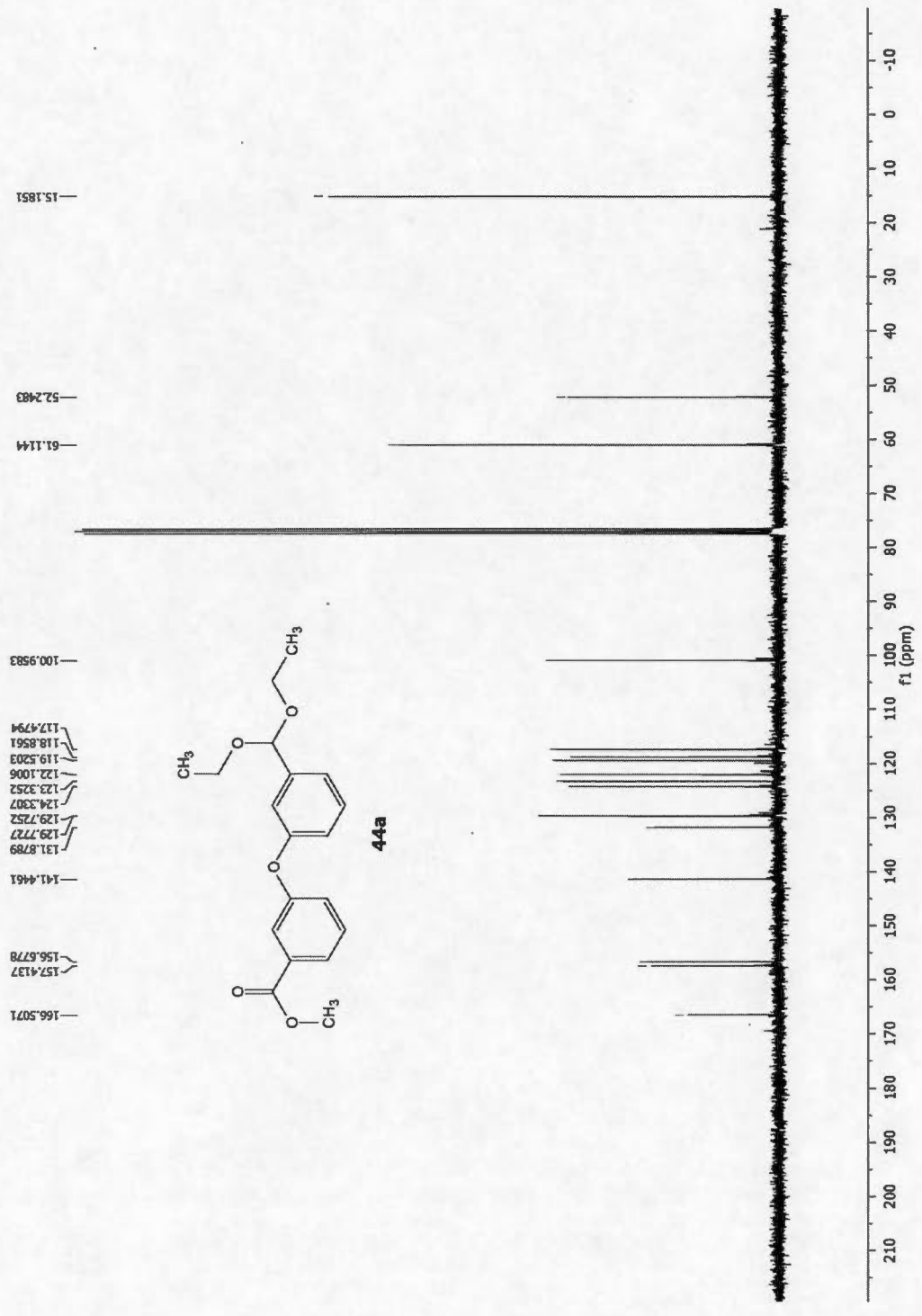

%Transmission
Nombre d'onde (cm-1)
40b
3289,01
3140,70
3117,88
3064,64
2926,34
2863,10
1685,20
1585,36
1605,88
1533,38
1488,99
1454,03
1399,59
1362,27
1255,39
1228,12
1048,87
790,96
755,01
696,69

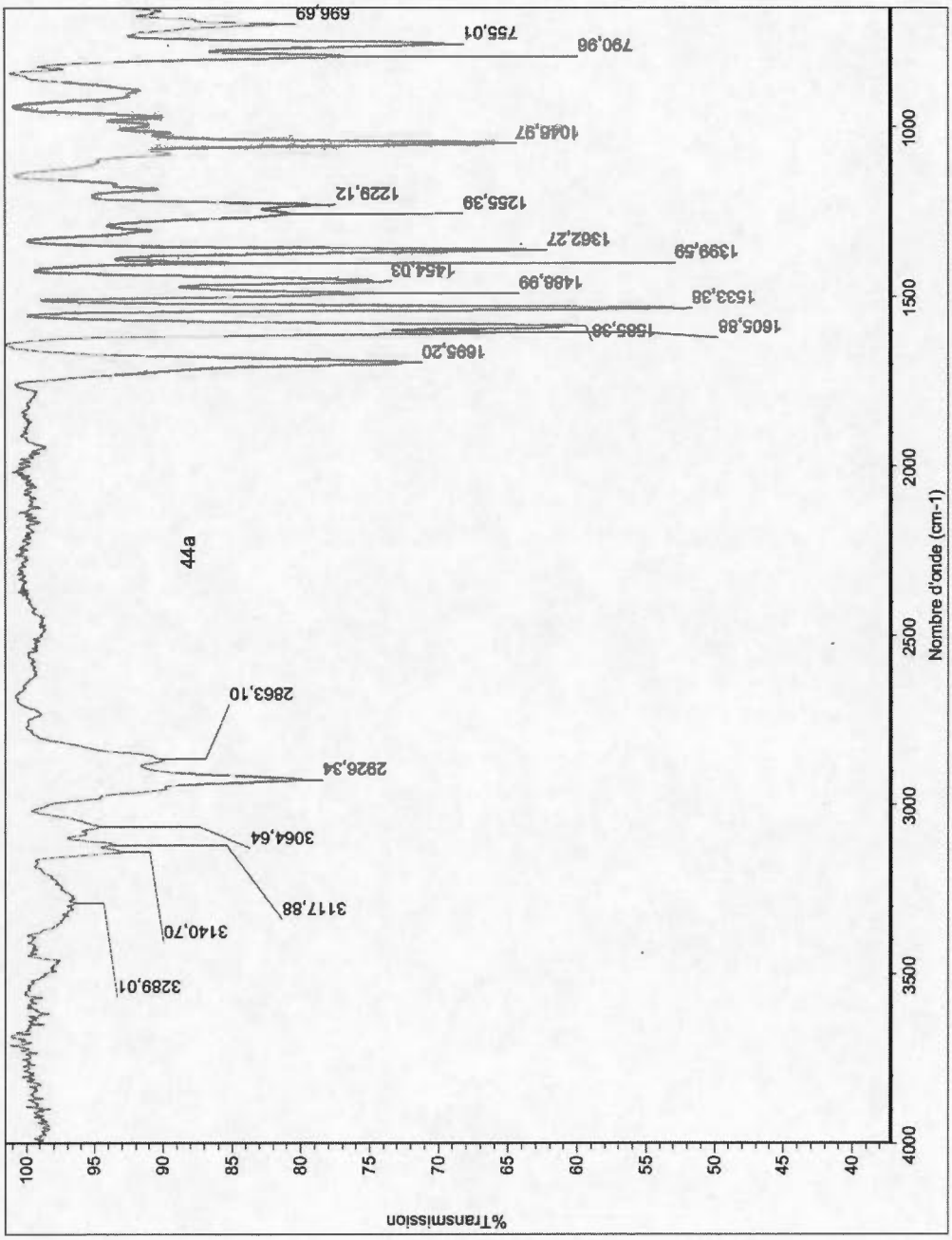

41a
f1 (ppm)

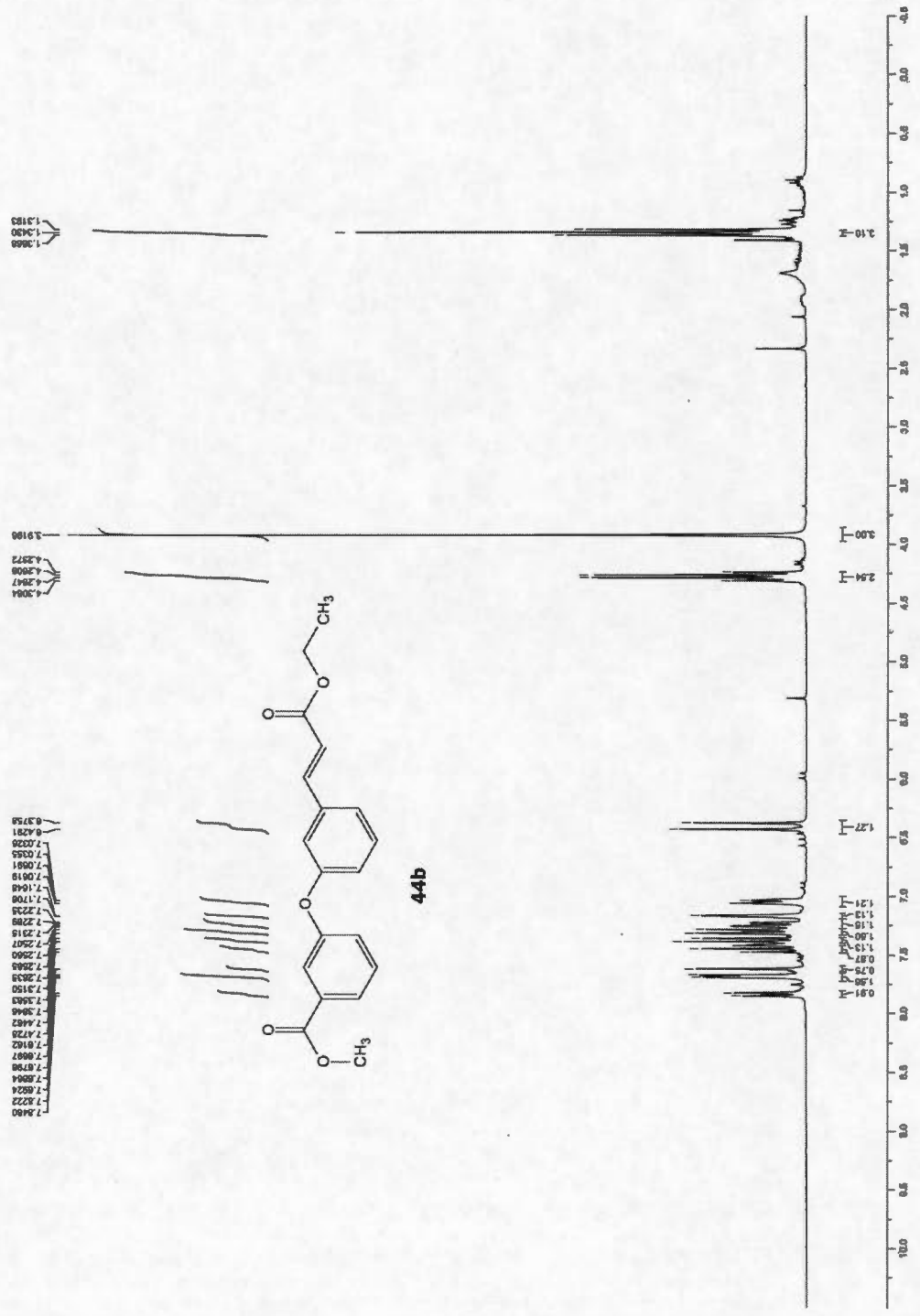
14.2948
60.7894
105.6714
106.9388
115.2147
120.4032
125.4607
127.6040
128.8737
130.1960
136.2770
140.0180
142.5110
142.7826
147.8687
159.1711
166.4070
CH3
O
O
N
O
N
41a
f1 (ppm)

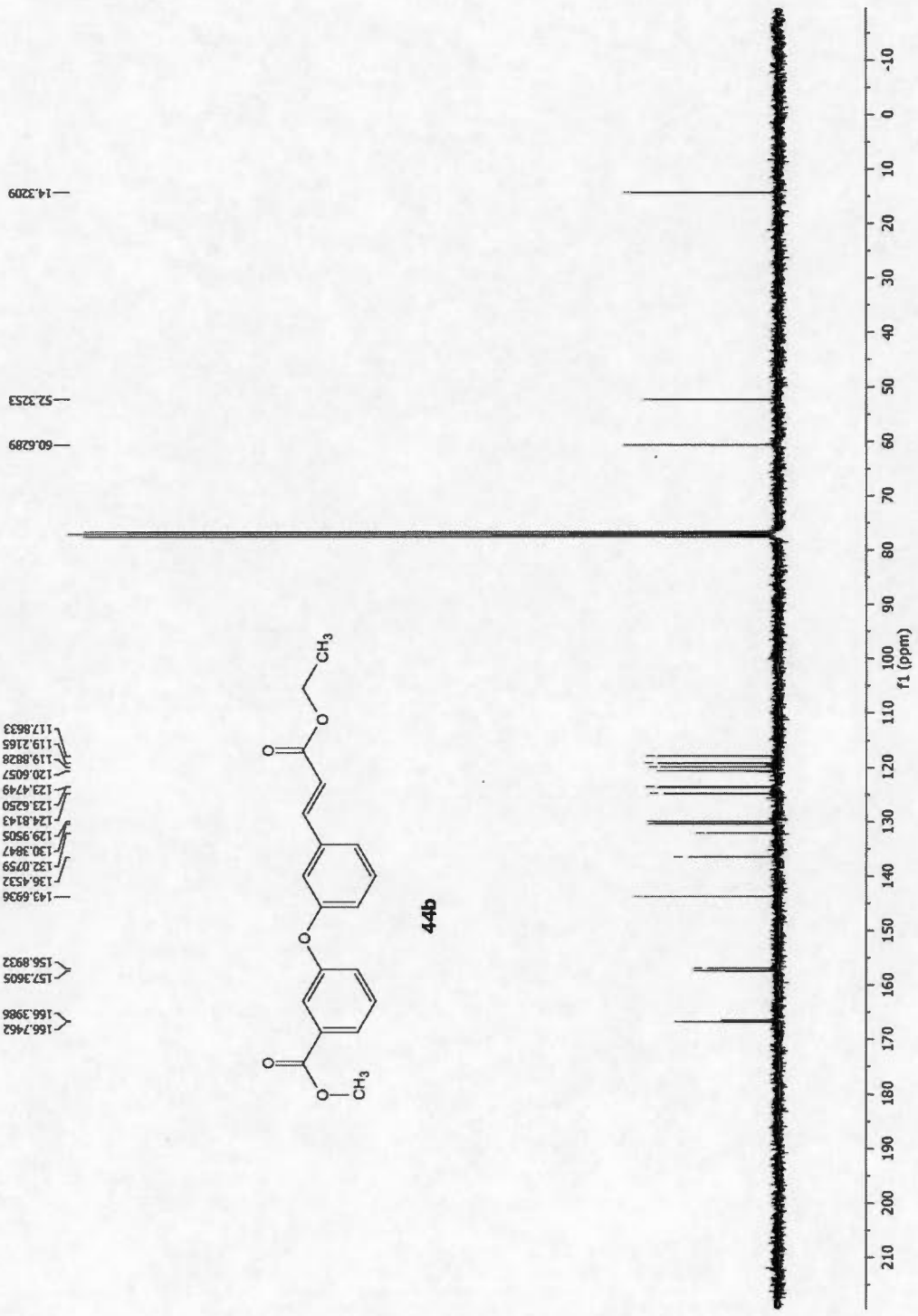

41a
%Transmission
Nombre d'onde (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
4000
3500
3000
2500
2000
1500
1000
3289,01
3140,70
3117,88
3064,64
2926,34
2863,10
1695,20
1605,88
1565,38
1533,38
1488,99
1454,03
1399,59
1362,27
1255,39
1228,12
1046,97
790,98
755,01
696,69

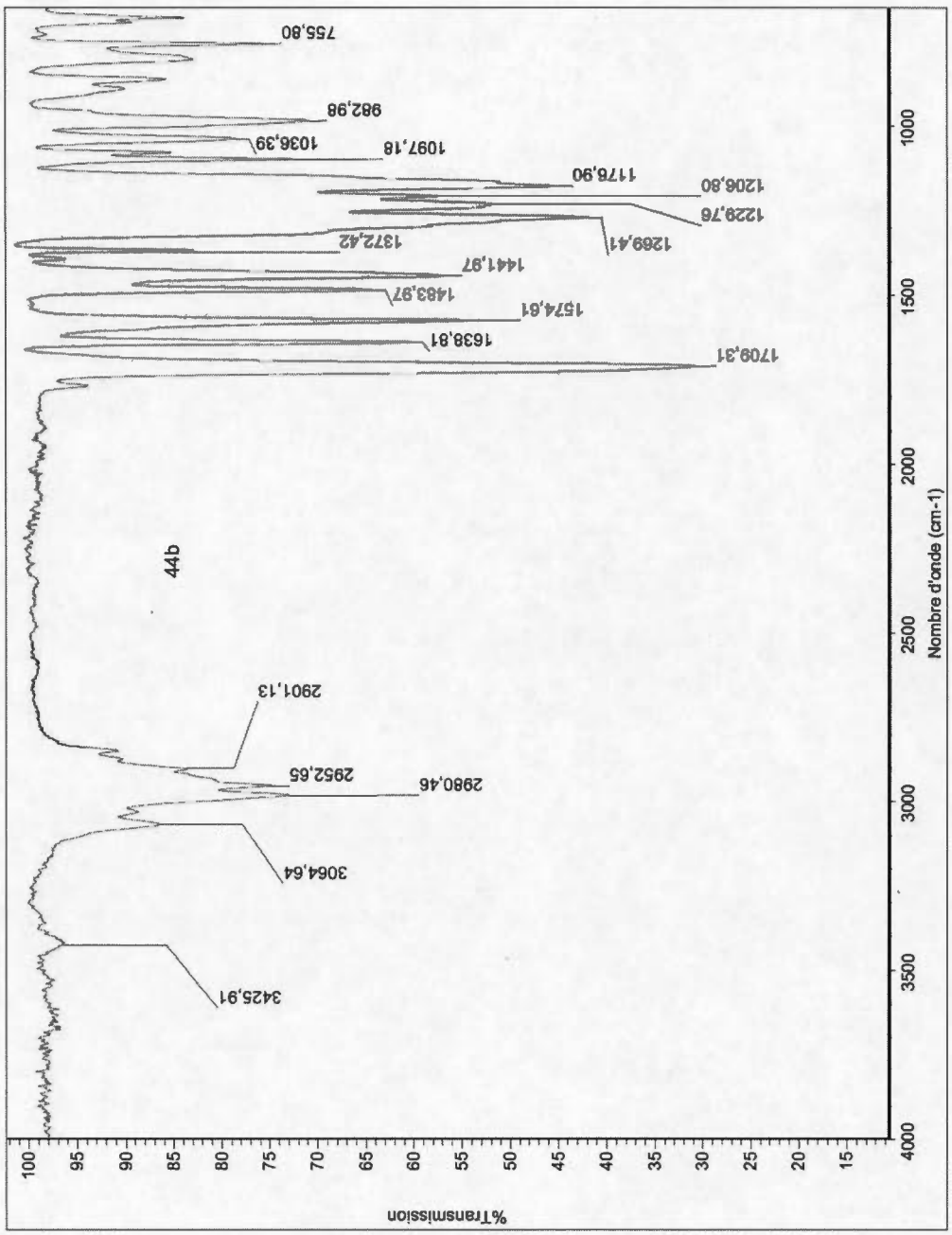

44a
f1 (ppm)

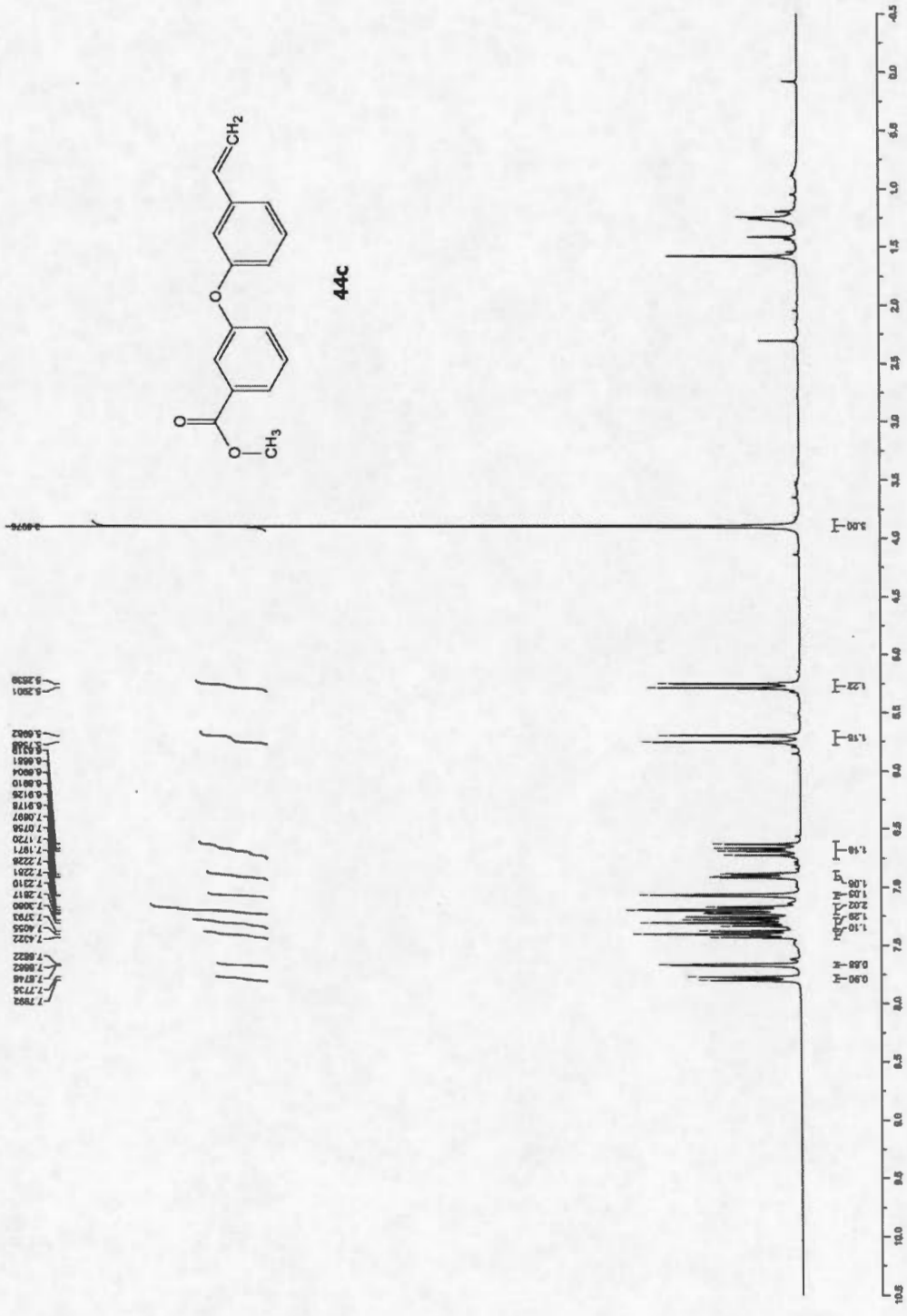

15.1851
52.2483
61.1144
100.9583
117.4794
118.8561
119.5203
122.1006
123.3252
124.3307
129.7252
129.7727
131.8789
141.4461
156.6778
157.4137
166.5071
44a
f1 (ppm)


%Transmission
100
95
90
85
80
75
70
65
60
55
50
45
40
4000
3500
3000
2500
2000
1500
1000
Nombre d'onde (cm-1)
44a
3289,01
3140,70
3117,88
3064,64
2826,34
2863,10
1695,20
1585,36
1605,88
1533,38
1488,99
1454,03
1399,59
1362,27
1255,39
1229,12
1048,97
790,96
755,01
696,69

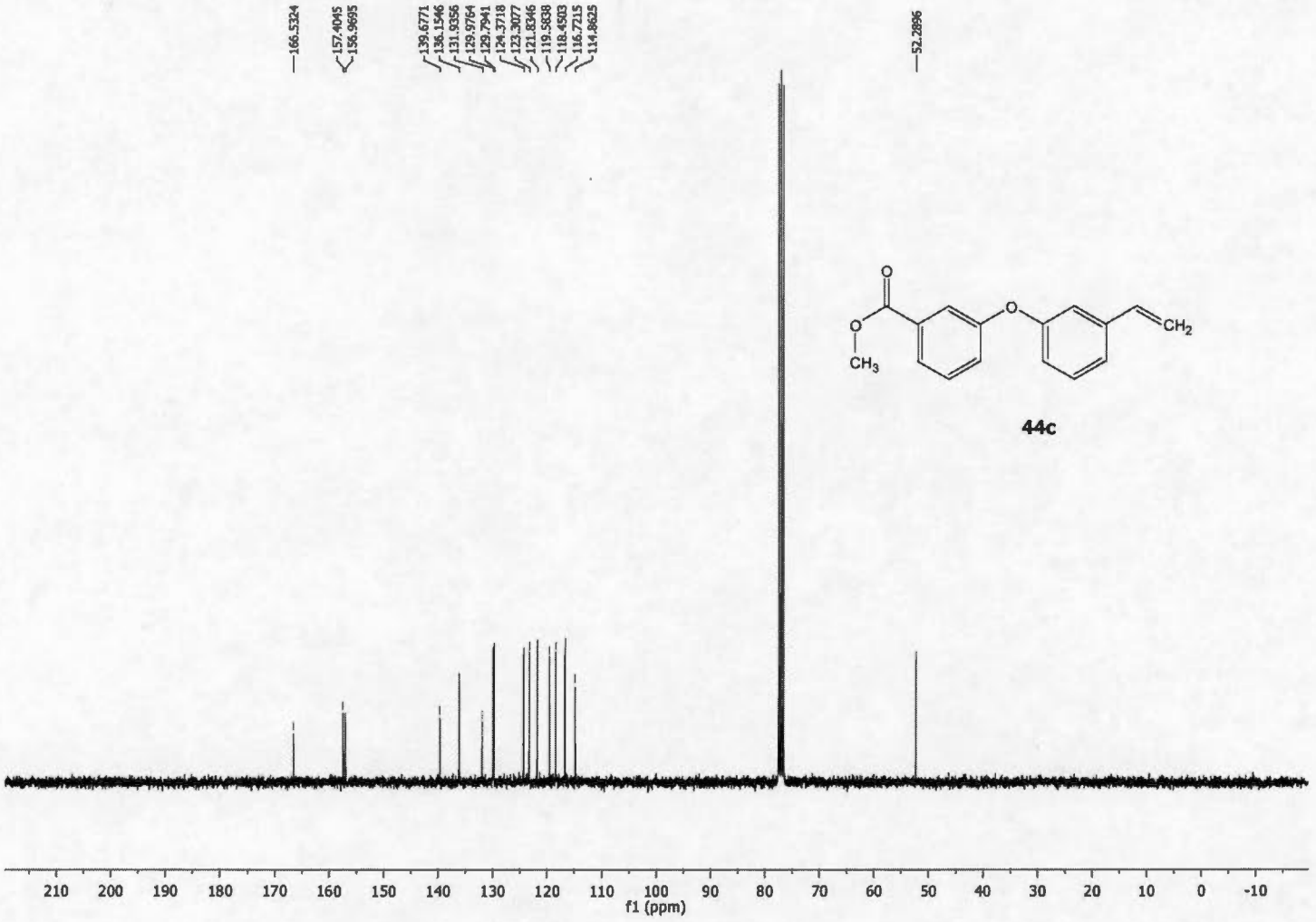

44b

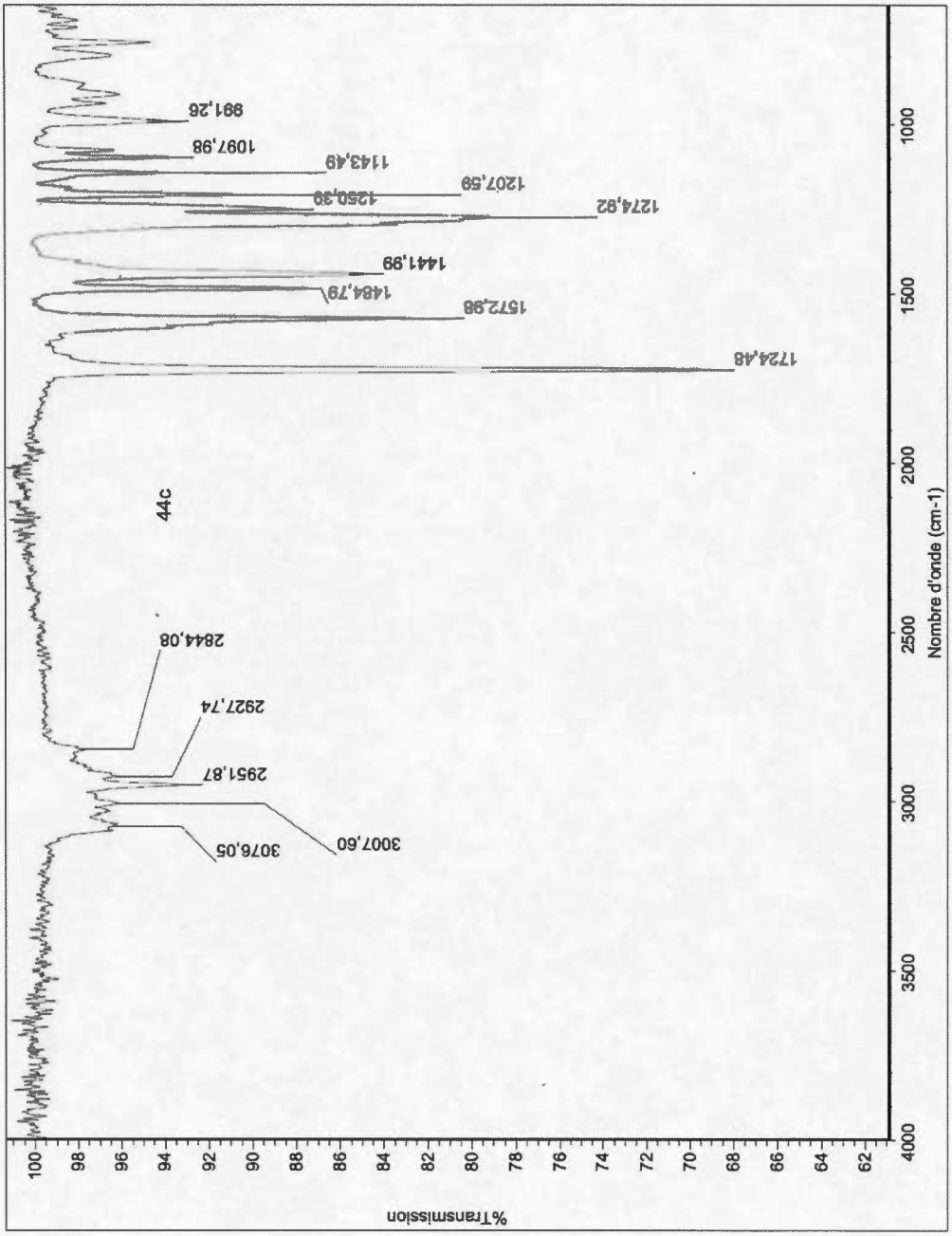

14.3209
52.3253
60.6289
117.8633
119.2165
119.8828
120.6057
123.4749
123.6250
124.8143
129.9505
130.3847
132.0759
136.4532
143.6936
157.3605
156.8932
166.3986
166.7462
CH3
O
O
O
O
CH3
44b
f1 (ppm)

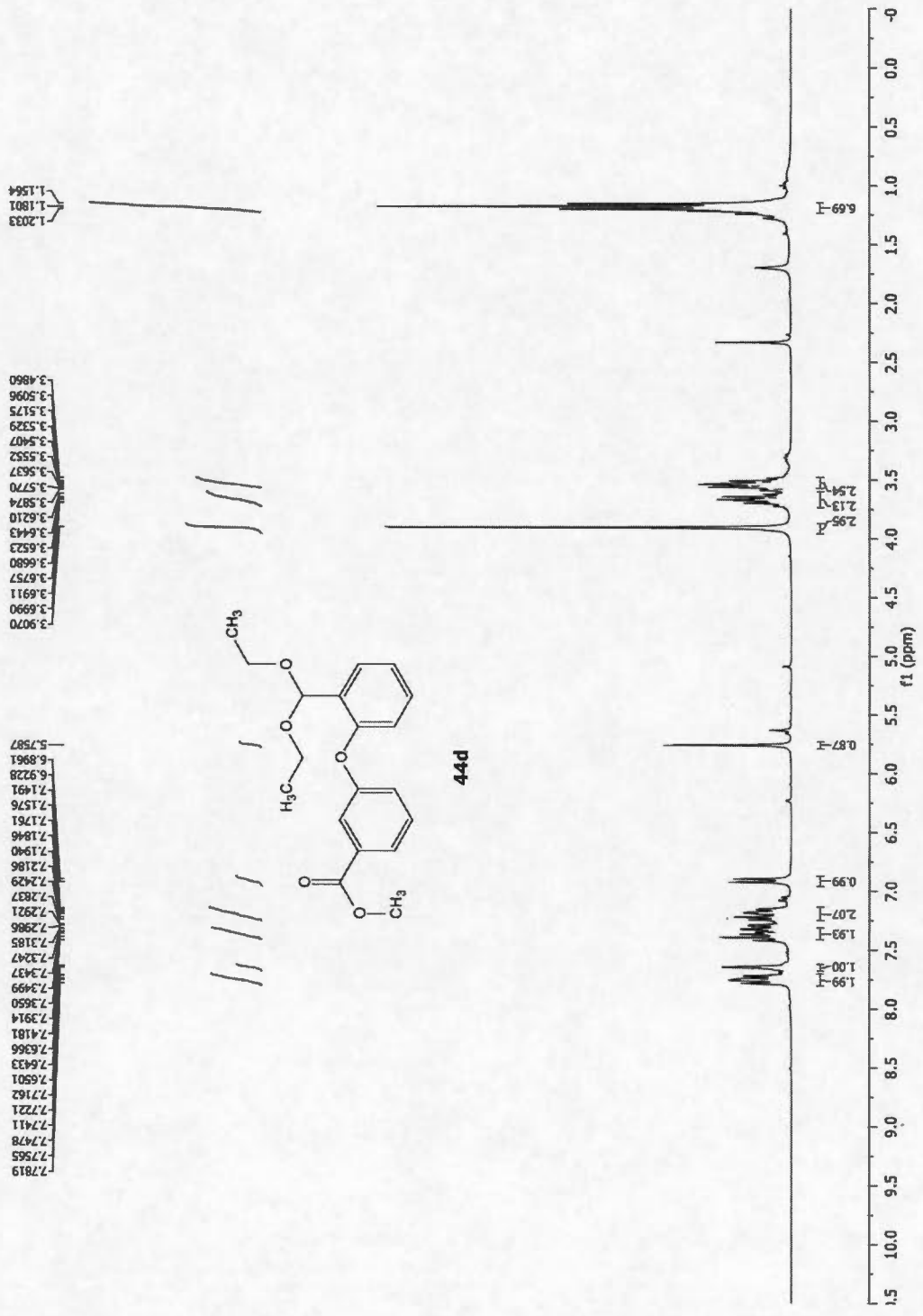

%Transmission
Nombre d'onde (cm-1)
44b
3425,91
3064,64
2980,46
2952,65
2901,13
1709,31
1638,81
1574,61
1483,97
1441,87
1372,42
1289,41
1229,76
1206,80
1176,90
1097,18
1036,39
982,98
755,80

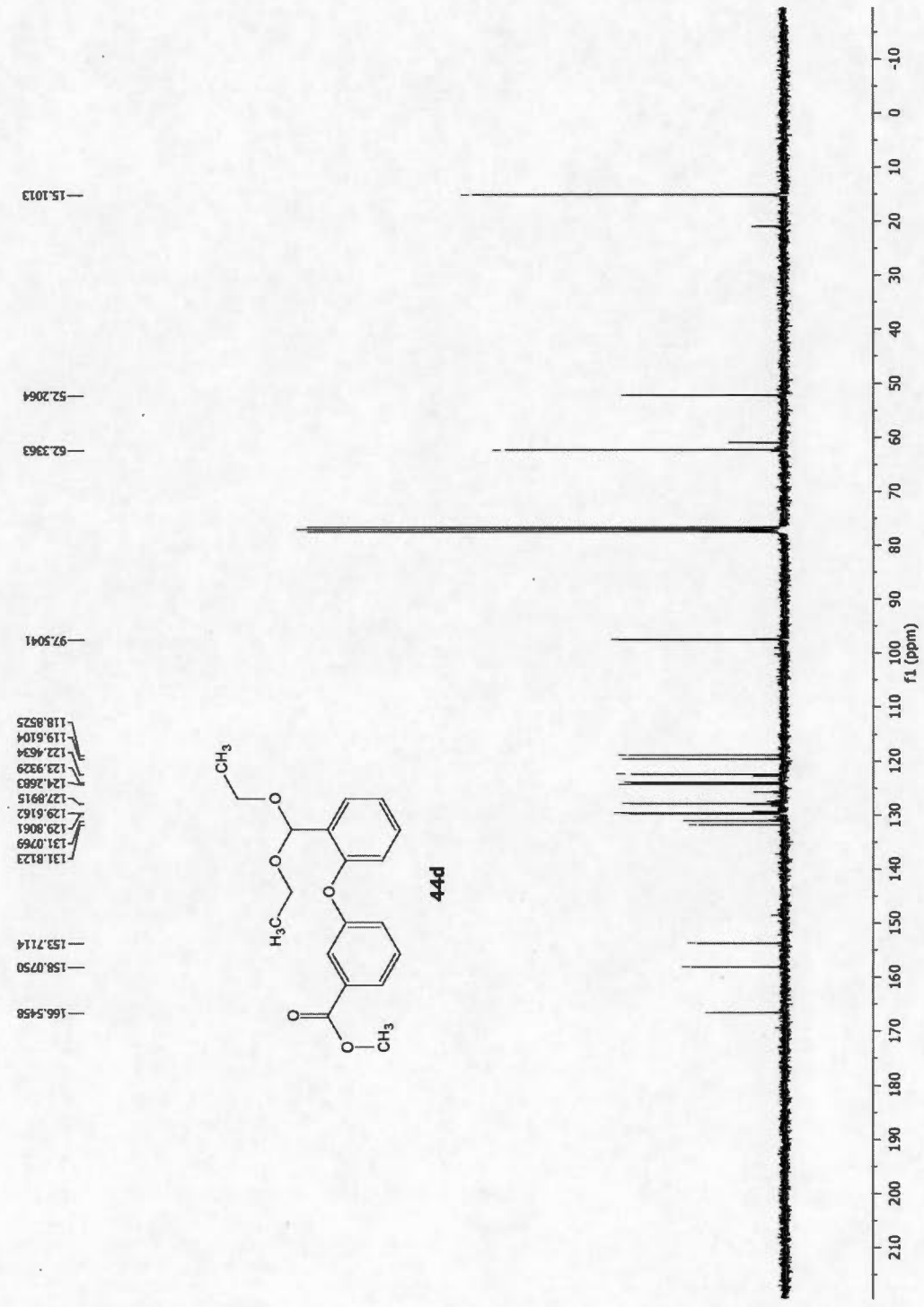


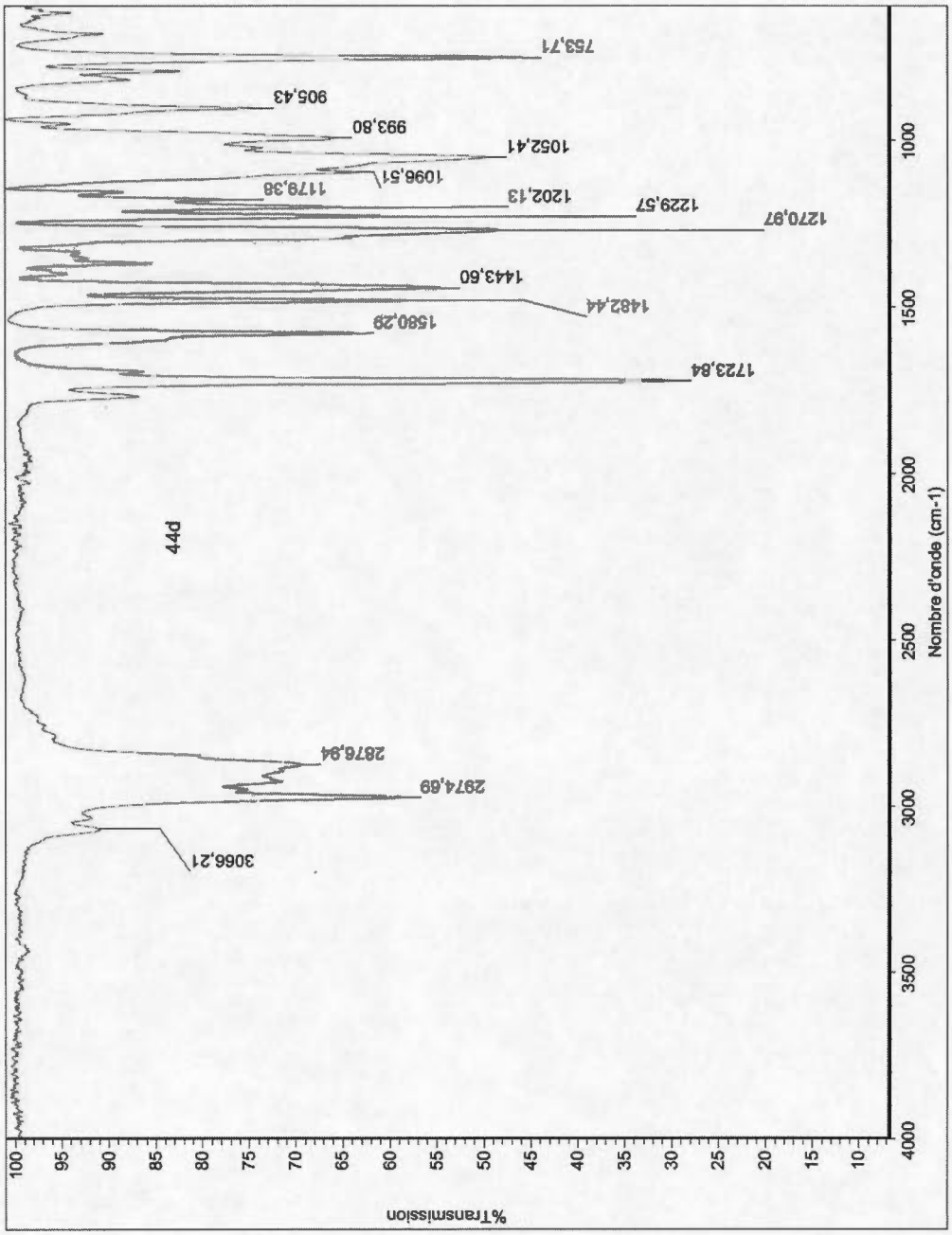
44c

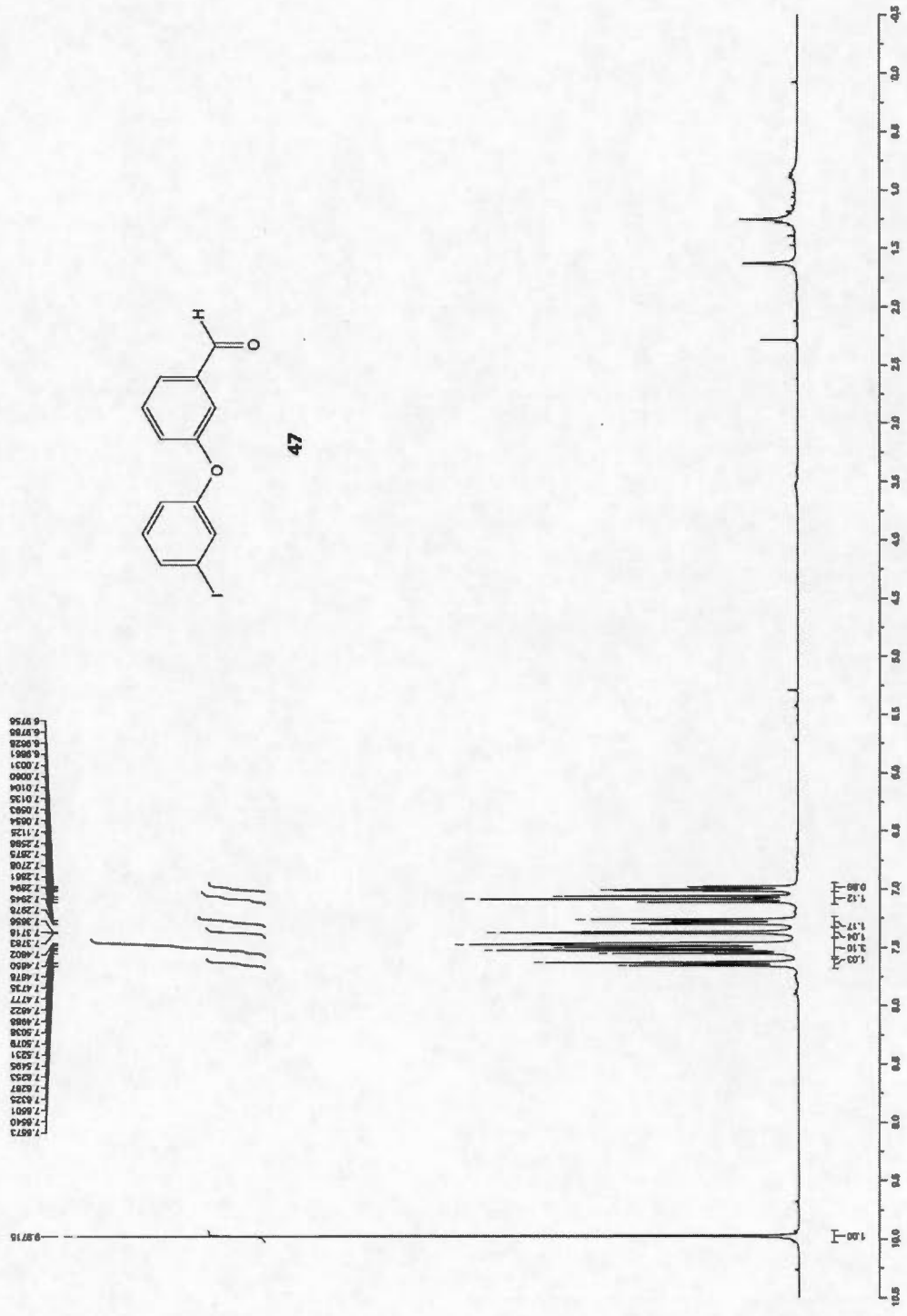

166.5324
157.4045
156.9695
139.6771
136.1546
131.9356
129.9764
129.7941
124.3718
123.3077
121.8346
119.5838
118.4503
116.7215
114.8625
52.2896
O
O
O
CH3
CH2
44c
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

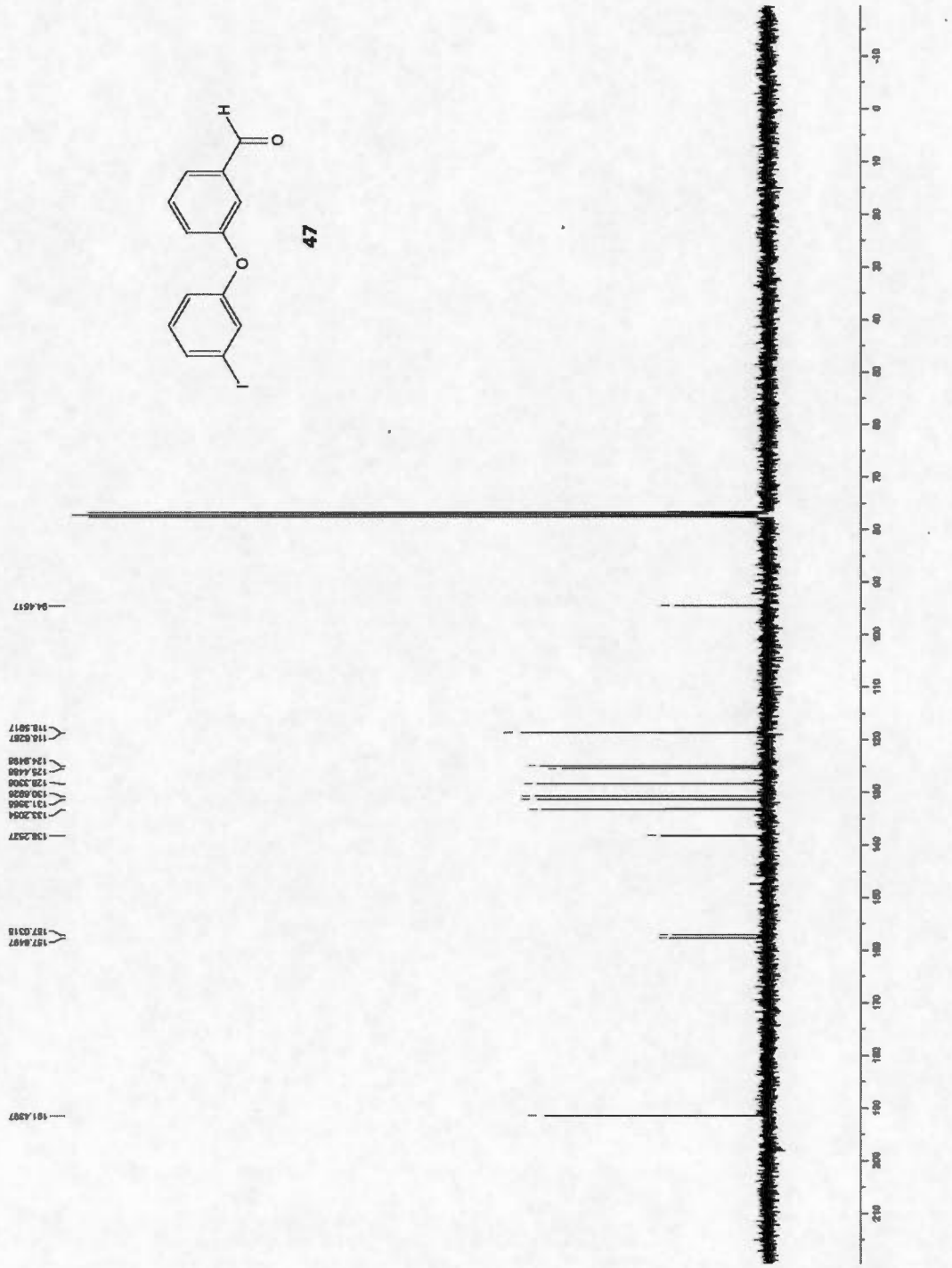

%Transmission
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64
62
4000
3500
3000
2500
2000
1500
1000
Nombre d'onde (cm-1)
44c
3076,05
3007,60
2951,87
2927,74
2844,08
1724,48
1572,98
1484,79
1441,99
1274,92
1250,39
1207,59
1143,49
1097,98
891,26

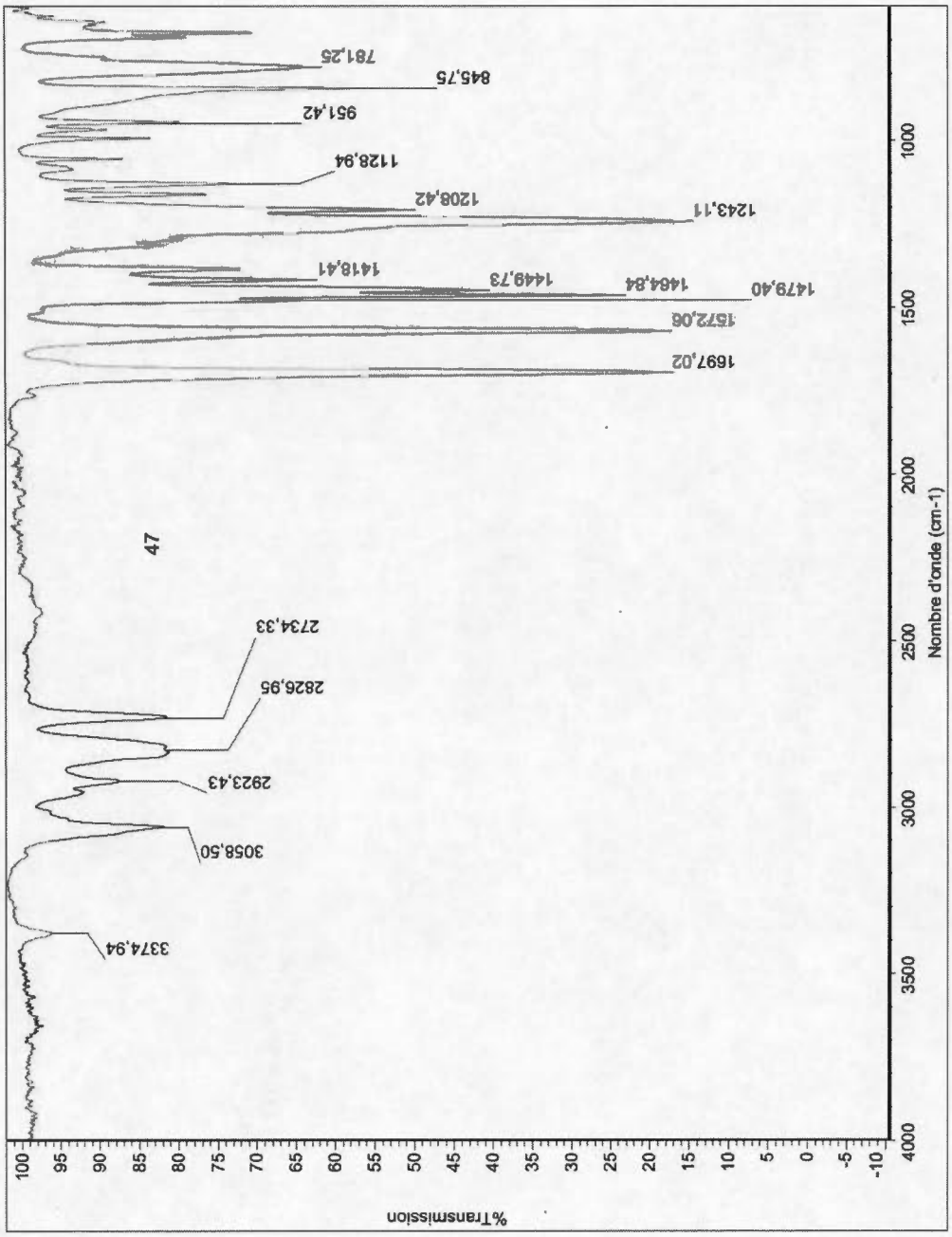

44d
f1 (ppm)

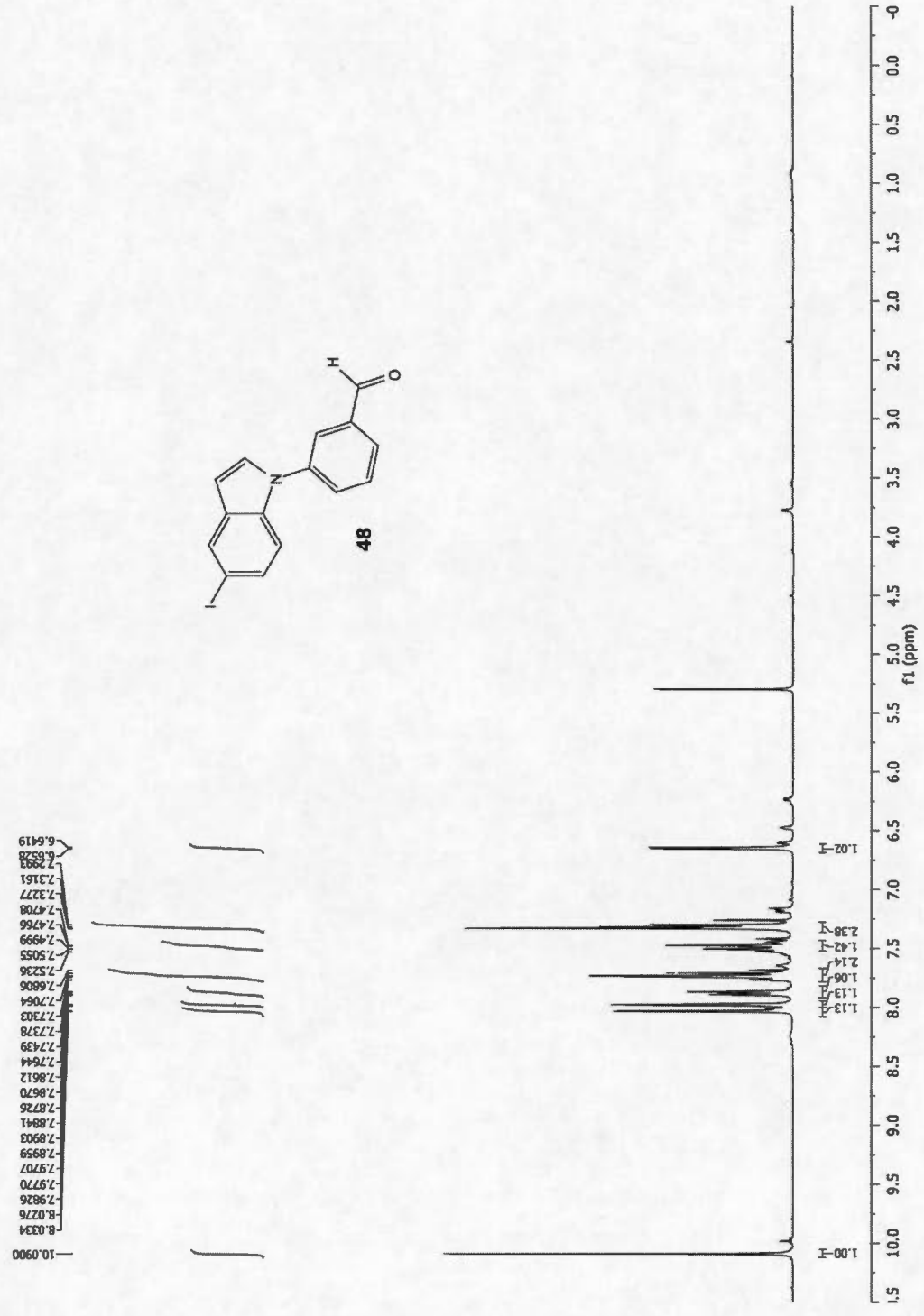

166.5458
158.0750
153.7114
131.8123
131.0769
129.8061
129.6162
127.8915
124.2683
123.9329
122.4634
119.6104
118.8525
97.5041
62.3363
52.2064
15.1013
44d
f1 (ppm)


%Transmission
Nombre d'onde (cm-1)
44d
3066,21
2974,89
2876,94
1723,84
1580,29
1482,44
1443,60
1270,87
1229,57
1202,13
1178,38
1096,51
1052,41
993,80
905,43
753,71


47


47
O
H
O
I
191.4397
157.8497
157.0318
138.2537
135.2094
131.3664
130.6826
128.3306
125.4486
124.3458
118.6287
118.5017
94.4617


%Transmission
Nombre d'onde (cm-1)
47
3374,94
3058,50
2923,43
2826,95
2734,33
1697,02
1572,06
1479,40
1464,84
1449,73
1418,41
1243,11
1208,42
1128,94
951,42
845,75
781,25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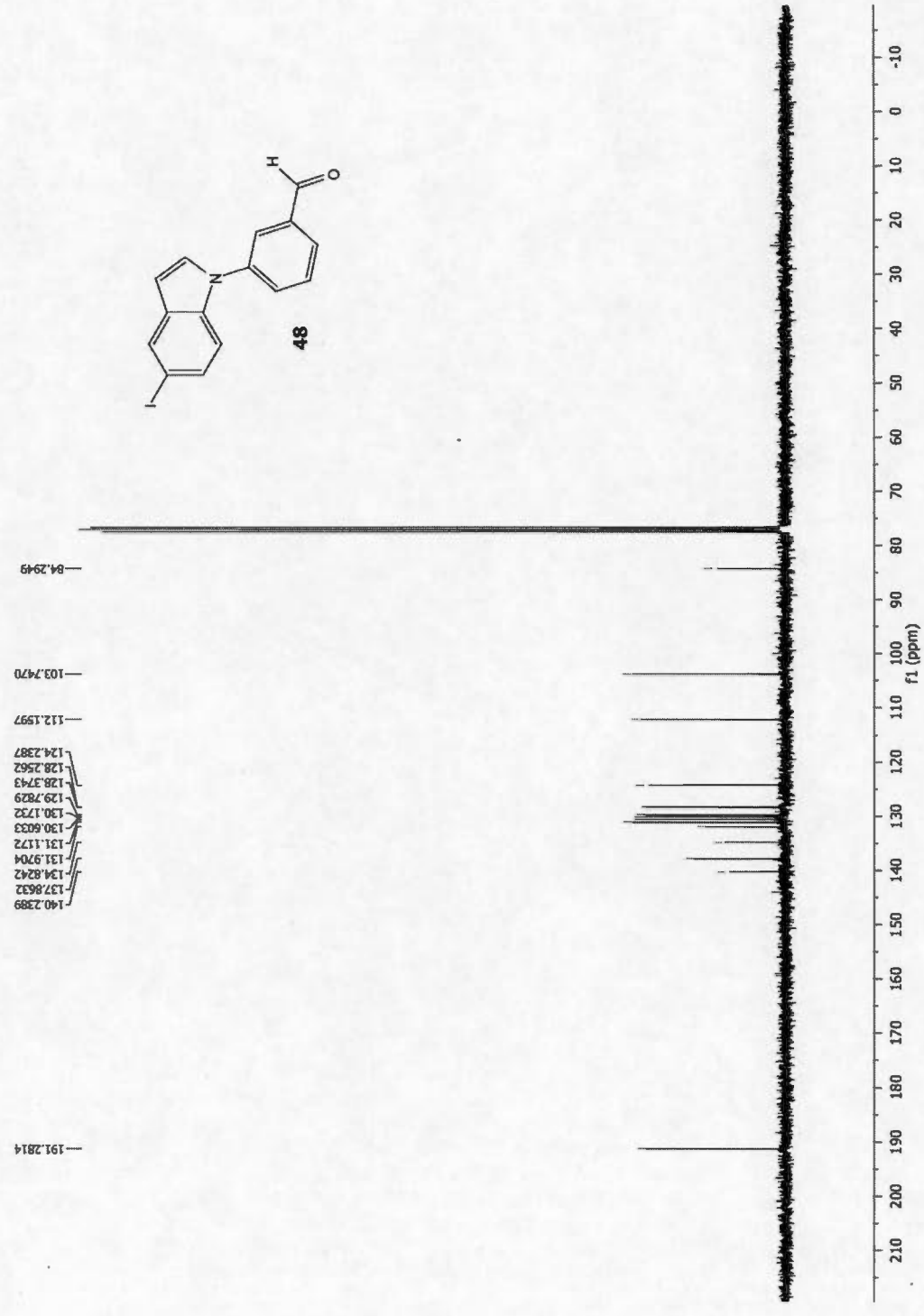
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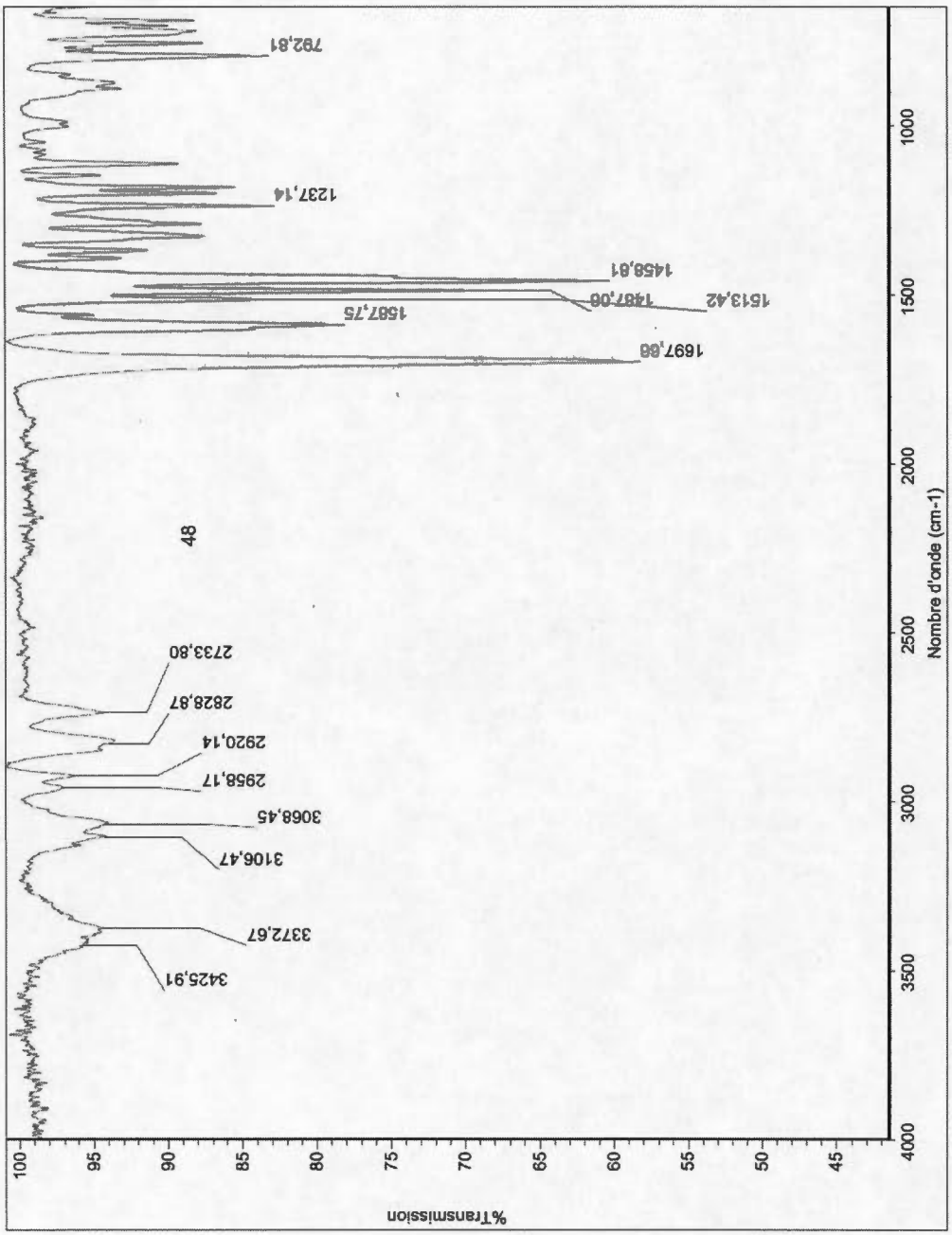
f1 (ppm)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1000
Nombre d'onde (cm-1)
48
3425,91
3372,67
3106,47
3068,45
2958,17
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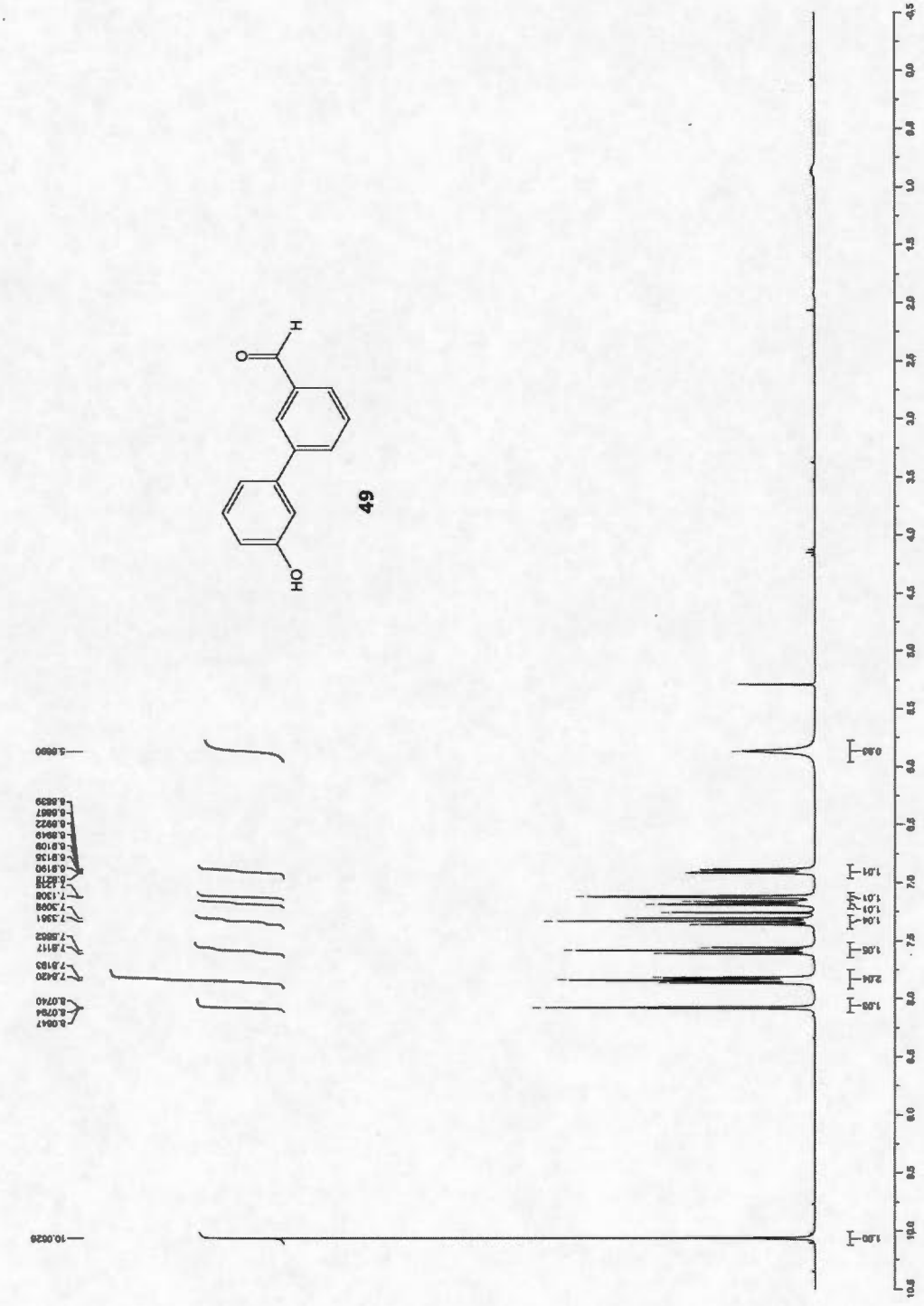
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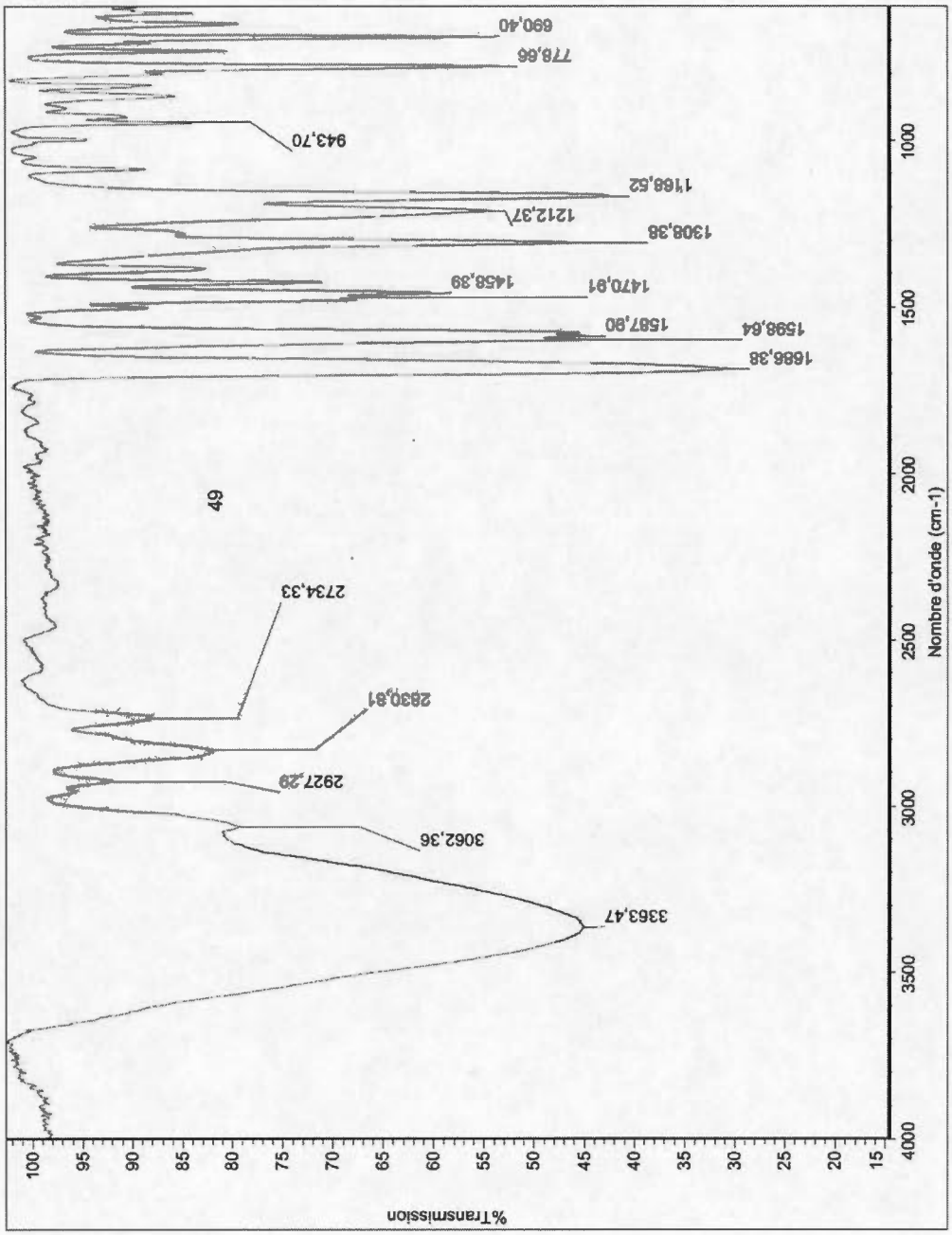
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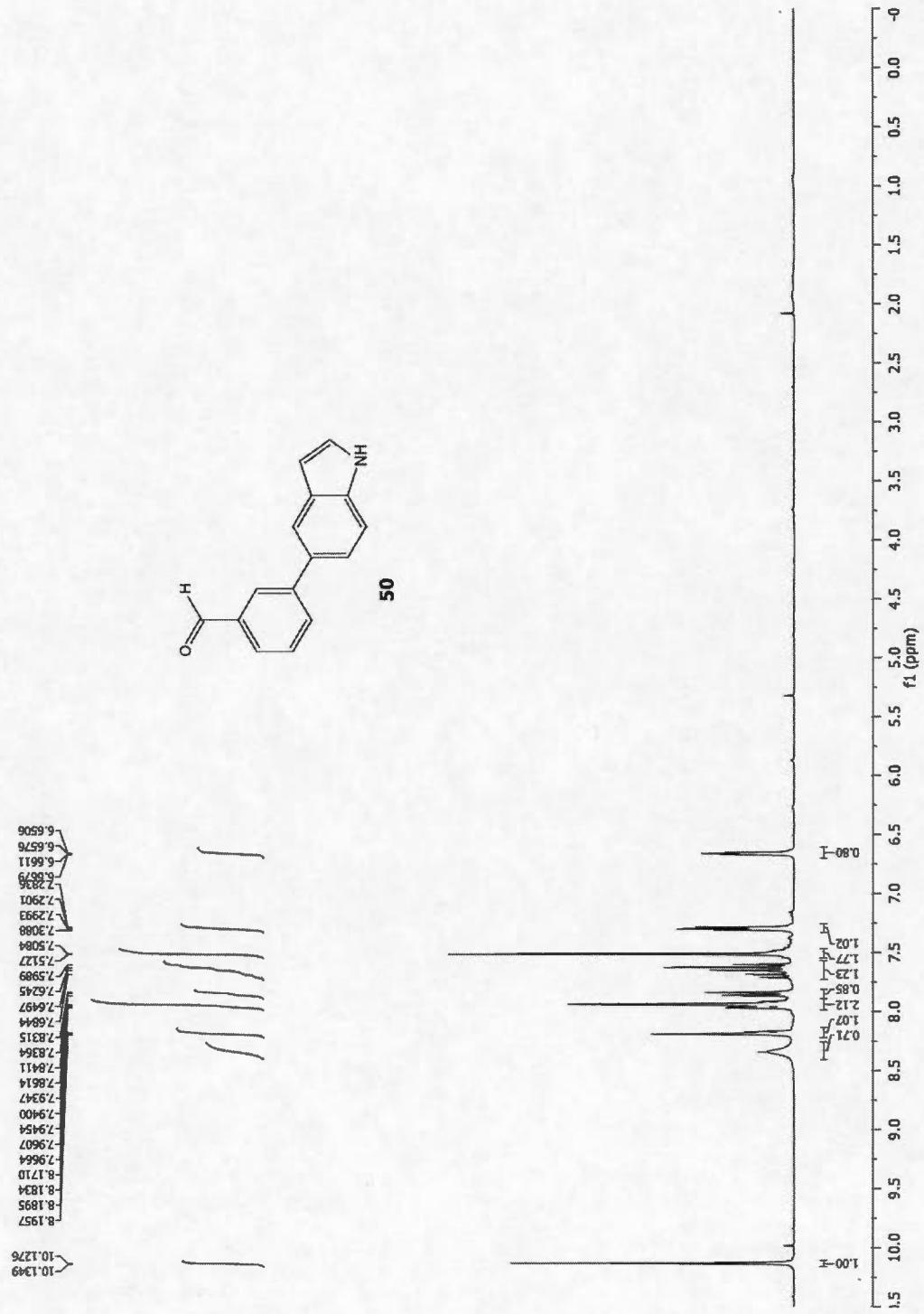
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H
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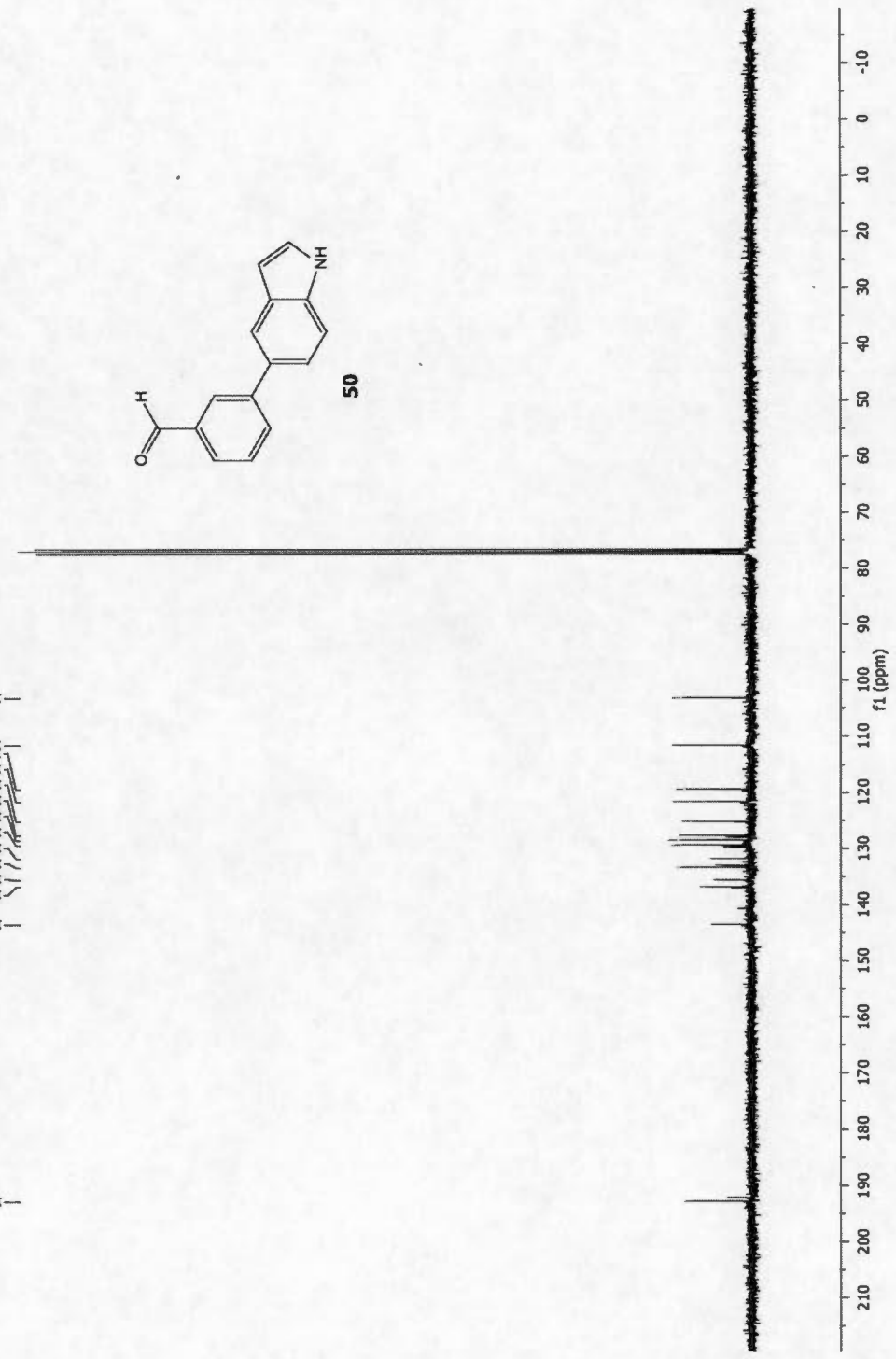
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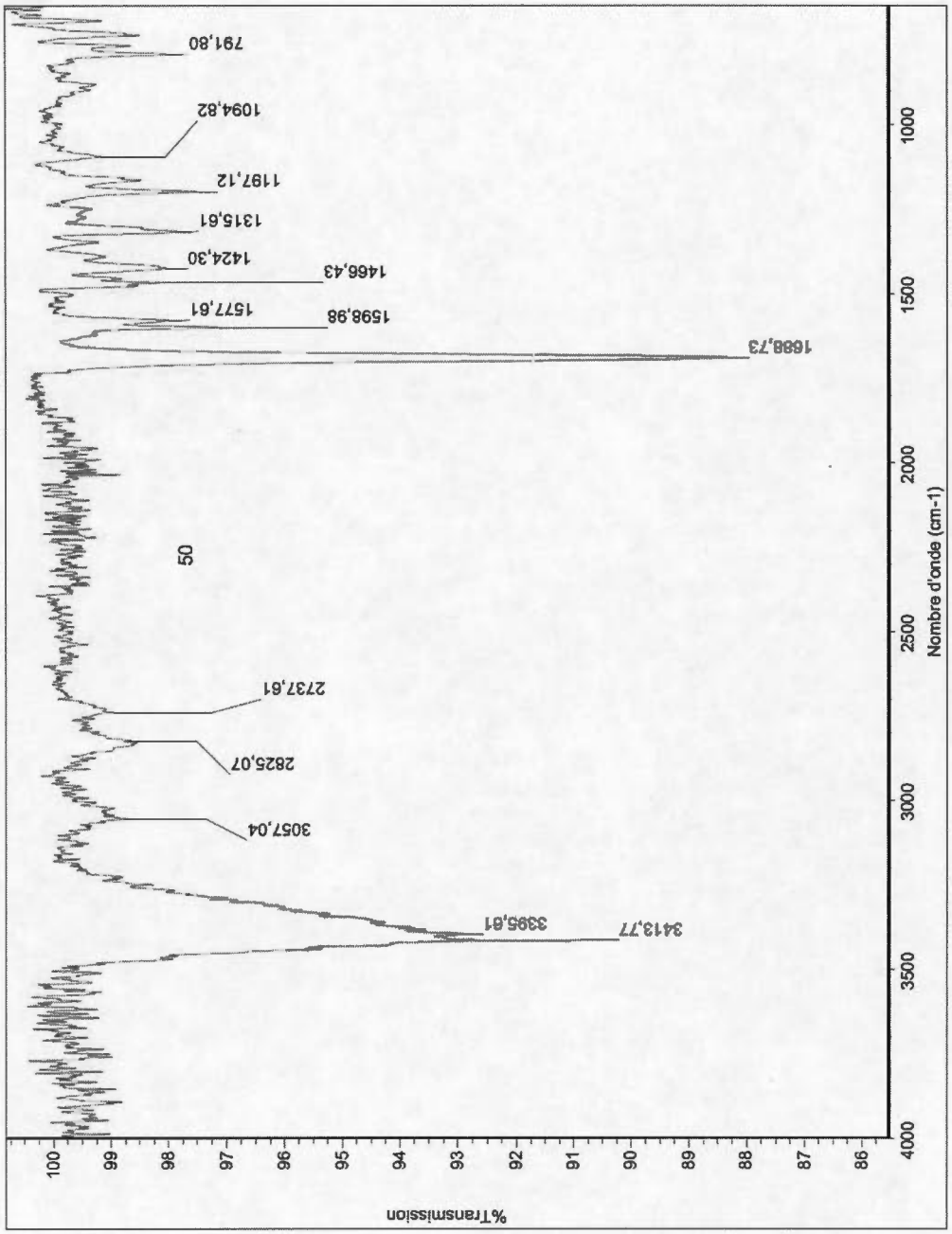
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